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PALLIATION OF CARCINOMATOSIS WITH ASCITES BY MEANS OF HEMISULFUR MUSTARD (2-CHLORO-2'-HYDROXYDIETHYL SULFIDE)*

ALEXANDER M. RUTENBURG, M.D.,† AND ARNOLD M. SELIGMAN, M.D.‡

BOSTON, MASSACHUSETTS, AND BALTIMORE, MARYLAND

THE preparation of hemisulfur mustard, the rationale that led to discovery of its palliative properties and its effect after administration to patients with malignant tumors have been reported.§ When palliation was observed, it generally consisted of suppression of ascitic-fluid formation in patients with peritoneal carcinomatosis as well as decrease in size of any tumor masses present, and of decrease in pain and increase in appetite, strength and ability to get around. The greatest benefit was observed in patients with carcinoma of the ovary.

The present report deals with improvement in the method of administration and presents the results of treatment of 30 additional patients with inoperable, recurrent and metastatic cancer no longer responsive to radiation or other therapy. Of these patients 14 had carcinomatosis of ovarian, and 1 carcinomatosis of endometrial origin.

TYPE OF PATIENT

Patients selected for treatment with hemisulfur mustard either were inoperable and unsuitable for radiation or had received the maximum dose of radiation or had become refractory to further radiation therapy. Most of the patients were in the terminal stage of their disease.

In view of our prior experience with the preparation in the suppression of ascites due to peritoneal metastases an effort was made to obtain patients with recurrent ascites who required frequent paracenteses to maintain reasonable comfort.

All patients had either palpable masses readily accessible to biopsy or other objective evidence of the extent of their disease such as ascites, pulmonary or skeletal metastases, or tumor cells in the peritoneal or pleural exudate.

PREPARATION OF PATIENT FOR TREATMENT

In view of the neurotoxic reactions that follow intravenous administration of hemisulfur mustard all patients received Dilantin (0.1 gm. three times daily) for three days before treatment. Dilantin was also continued during treatment. One hour before each injection patients also received subcutaneously or intramuscularly chlorpromazine (Thorazine), 25 mg., a barbiturate, 0.1 gm., and Demerol, 50-100 mg., or morphine sulfate, 8-10 mg.

METHOD OF ADMINISTRATION

Hemisulfur mustard¶ was supplied in solution in dry ether in sealed glass ampoules, which were stored at −10 to −20°C. The concentration in each batch of ampoules varied from 90 to 120 mg. per milliliter and was determined periodically by evaporation in vacuo of 2 ml. in a tared vessel. At the bedside the dry-ether solution (1-4 ml.), equivalent to about 100 to 400 mg. of hemisulfur mustard, was withdrawn with a needle and syringe from the ampoule and immediately added to 50 ml. of sodium chloride solution (0.85 per cent) and vigorously agitated by aspiration with some air into a 50-ml. syringe. The resulting opalescent solution was then rapidly injected (within sixty seconds) through polyethylene tubing that had been inserted into the superior vena cava via the brachial vein. After the injection the tubing was flushed with sodium chloride solution (0.85 per cent). The polyethylene tubing was kept patent by injection of 1 to 1.5 ml. of heparin (10 mg. per milliliter), and the end of the tubing was kept sealed by means of a Tuohy adapter. The tubing, adapter and wound were protected with a dry sterile dressing. The physician handling the administration was careful to avoid

*From the departments of Surgery, Beth Israel Hospital and Harvard Medical School, Boston, and Sinai Hospital of Baltimore and Johns Hopkins University School of Medicine, Baltimore.

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†Associate in surgery, Harvard Medical School; associate visiting surgeon and associate director of surgical research, Beth Israel Hospital.

‡Associate professor of surgery, Johns Hopkins University School of Medicine; surgeon-in-chief, Sinai Hospital of Baltimore.

§Seligman, A. M., Rutenburg, A. M., Persky, L., and Friedman, O. M. Effect of 2-chloro-2'-hydroxydiethyl sulfide (hemisulfur mustard) on carcinomatosis with ascites. *Cancer* **5**:354-363, 1952.

¶Available from Dajac Laboratories, Chemical Division, Borden Company, 511 Lancaster Street, Leominster, Massachusetts. This material is stored in dry ether in sealed glass ampoules and must be kept under refrigeration at −10 to −20°C. It is also necessary to ship it by air express on dry ice.

getting it on the skin of the patient and on his own skin because of its marked vesicant action, which we have observed on a few occasions. The use of warm syringes or excessive handling when transferring the ether solution was avoided to prevent accidental forceful ejection of the ether solution onto the skin or into the eyes.

TABLE 1. *Toxic Reactions Encountered in 30 Patients.*

TYPE OF REACTION	NO. OF PATIENTS
Malaise & weakness	30
Nausea & vomiting	30
Axillary thrombophlebitis & edema	3
Tremor	5
Convulsions	2
Dizziness, dysarthria & diplopia	1
Vascular collapse	1

DOSAGE

The initial dose was 100-200 mg. This was subsequently increased in later doses to 300 or 400 mg., depending on the ability of the patient to tolerate the drug. In weak, debilitated patients in the last stage of their disease, the initial dose was only 100 mg., and the subsequent dose was 200 mg. Most of the patients received three or four doses at intervals of two to four days, depending on the nature and severity of the reaction after administration and depending on the age and debility of the patient. A second dose was not administered until all toxic effects of the first dose had largely subsided.

TOXIC REACTIONS

Malaise, weakness, nausea and vomiting uniformly followed administration of hemisulfur mustard (Table 1). Injections of the drug through polyethylene tubing placed in the superior vena cava eliminated the severe local reaction and thrombophlebitis that had been observed after injection into a peripheral vein in the earlier series referred to above. Axillary-vein thrombosis and swelling of the arm only occasionally developed after prolonged (fifteen to twenty days) utilization of the polyethylene tubing for intravenous administration of solutions. This promptly subsided when the tubing was removed.

Other reactions, consisting of gastrointestinal symptoms and neurotoxic and vascular collapse, are described below.

Gastrointestinal Symptoms

Nausea and vomiting occurred half an hour after injection and persisted for five to twenty-four hours. This was severe in some patients whereas others showed very little nausea and no vomiting. The severity of this reaction could be substantially suppressed by prior administration of chlorpromazine and barbiturates. Chlorpromazine was found to be considerably more effective than Dramamine.

Neurotoxic Symptoms

A tremor of hands, fingers and toes occurred in 5 patients. This usually followed the second or third dose and subsided spontaneously forty-eight to seventy-two hours after the last injection. Convulsions occurred in 2 patients, 1 of whom had not received Dilantin before treatment. These convulsive episodes were clonic in type and of short duration. In 1 patient (Case 8) a coarse intention tremor, dizziness, diplopia and dysarthria followed the third injection. These persisted for three days and then disappeared spontaneously without any residue. The same patient received a second course eight months later, without any undue neurotoxicity.

Vascular Collapse

Severe vascular collapse or deep shock occurred twenty-four hours after the second injection in a patient with ovarian carcinoma and peritoneal carcinomatosis who had in addition intestinal obstruction due to involvement of loops of small and large bowel in the tumor mass. Shock persisted for several days, during which supportive therapy was given. Restoration of the hemodynamics to normal was gradually effected with blood, plasma, nor-epinephrine drip and antibiotics.

Patients with even less extensive intestinal obstruction tolerated hemisulfur mustard poorly and showed a tendency to hypotension and occasionally vascular collapse. Several such patients (not included in this series) could not tolerate the large doses that were considered desirable for effective therapy. However, after restoration of blood volume with blood or plasma and correction of electrolyte imbalance with vigorous parenteral therapy, the cautious administration of hemisulfur mustard in somewhat smaller doses (50-100 mg.) was tolerated.

There were no other toxic reactions. The striking lack of adverse effect on the hematopoietic system was observed in this group of patients as well as in the previous series, and no depression of liver or renal function, as determined by routine standard laboratory tests, was observed in many of the patients so tested.

RESULTS

No beneficial effect whatsoever was observed in 16 of these 30 patients. Fourteen patients were benefited (Table 2). Of these, 3 patients (Cases 8, 18 and 21) had the most striking palliation and responded initially for eight to twenty-eight months but showed no improvement with a second course administered some months after definite exacerbation of the pathologic process had occurred (Table 2). The other 11 patients were benefited for only three months, with suppression of ascites, increased strength, appetite and ability to get around and shrinkage of tumor masses, with decrease of any pain present. All the patients reported in this study have since died.

Suppression of Ascitic-Fluid Formation

Fourteen of 20 patients with peritoneal carcinomatosis and ascites (9 of 14 with ovarian carcinoma, 1 with endometrial carcinoma, 2 of 3 with carcinoma of the stomach, 1 of 3 with carcinoma of the colon and 1 with renal-cell carcinoma) showed a striking decrease in the accumulation of ascitic fluid for a period of three to eleven months, and 1 for twenty-nine months, as well as general palliation consisting of increased appetite, decreased pain and discomfort and a general sense of increased well-being and fitness. In 10 of 14 patients who improved, carcinoma cells were readily demonstrated in the ascitic fluid before the administration of hemisulfur mustard (Table 2). After treatment either carcinoma cells were not found in the small amount of peritoneal fluid aspirated or there was no available fluid for examination during the period when ascitic fluid failed to accumulate.

The most striking remission was observed in a patient (Case 21) with a mixed mesodermal tumor of the endometrium. Palliation was produced for a period of twenty-nine months, and she was free of all signs and symptoms of her initial disease during this period. Two abdominal operations performed during this period, hysterectomy and cholecystectomy, failed to disclose any gross evidence of tumor, which had previously been extensive. At the initial operation, before hemisulfur mustard therapy, she showed extensive intra-abdominal metastatic cancer involving the peritoneal surfaces of the bowel, as well as parietes, and the omentum was solid with infiltrating carcinoma (Fig. 1). The primary source was not discernible at operation. However, some sixteen months later, she was readmitted to the hospital because of vaginal bleeding, and a curettage (Fig. 2), followed by hysterectomy for a mixed mesodermal tumor of the endometrium, was performed (Fig. 3). This was assumed to be the primary source for the peritoneal metastases that had been suppressed, presumably by the initial course of hemisulfur mustard, although at operation for hysterectomy, as well as again six months later at the time of cholecystectomy for acute cholecystitis (Fig. 4), there was no gross evidence of intra-abdominal tumor. The peritoneal surfaces were smooth and glistening, and the omentum was soft and free of the previously observed infiltration. However, biopsy of omentum and peritoneum revealed nests of tumor cells, which in only some areas were encased in dense scar tissue (Fig. 3 and 4).

Carcinoma of the Ovary

As a group, the best results were observed in patients with carcinoma of the ovary. At operation all 14 of these patients had an inoperable ovarian carcinoma with extensive metastases to the visceral and parietal peritoneum. In addition 3 had liver metastases, and 2 of these also had pleural or pulmonary metastatic lesions. Nine of the 14 had had radiation therapy without a satisfactory response. In all cases there were rapid and recurrent ascitic-fluid formation and palpable abdominal masses. Palliation generally consisted of suppression of ascitic-fluid formation. This usually occurred about ten days after termination of therapy. In addition abdominal masses decreased in size. The patients felt stronger and more fit and had increased appetite and a sense of well-being during this period. Several previously bed-ridden patients were able to leave their beds and resume activity. Nine of the 14 patients in this group showed a beneficial response. Palliation, however, was temporary. The disease usually recurred and progressed after three to nine months, with a rapid increase in the size of metastatic masses, cachexia and death. Only rarely did ascites recur once it had been suppressed with hemisulfur mustard therapy even though there was exacerbation of the disease as shown by growth of intra-abdominal masses and progressive deterioration.

Carcinoma of the Gastrointestinal Tract

Three of 6 patients with carcinoma of the stomach (3 cases) or colon (3 cases) showed transient palliation. All 6 had been explored and found inoperable, with extensive peritoneal carcinomatosis and ascites.

The palliation, when it was observed, was similar to that described for patients with ovarian carcinoma. In addition, however, 2 of the 3 patients who responded showed a striking decrease in severe abdominal and back pain, which had been attributed to involvement of the celiac plexus.

Lymphoma

Five patients with malignant lymphoma failed to respond. Four of them had become refractory to radiation therapy before injection of hemisulfur mustard. The fifth patient (Case 24), with giant-follicle lymphoma, improved with nitrogen mustard (methyl *bis* [beta-chlorethyl] amine) and radiation therapy, after failing to be helped by hemisulfur mustard.

Case Reports

Case 1. A 67-year-old woman was admitted to the hospital with dyspnea, pain in the right side of the chest, fatigue, anorexia and progressive abdominal swelling. She was found to have a right-sided pleural effusion, ascites, enlarged liver and multiple large nodular masses in the pelvis and lower abdomen. Thoracentesis yielded 6 liters and paracentesis 3 liters of straw-colored fluid. The sediments contained tumor cells. Laparotomy showed an undifferentiated carcinoma involving both ovaries and extending to the cul-de-sac, rectosigmoid, bladder, broad ligaments, peritoneum, serosal surfaces of the viscera and omentum. The transverse mesocolon was filled with large tumor nodules. Oöphorectomy was not feasible because of the extent of the growth in the pelvis. Postoperatively pleural and ascitic fluid accumulated at such a rate as to require paracentesis and thoracentesis at intervals of 6 to 8 days to maintain relative comfort. On each occasion 2 to 4 liters of serous fluid was removed. Two days after the last paracentesis hemisulfur mustard (1140 mg.) was given

in 3 doses over a period of 9 days. After each injection transient vomiting and malaise developed. Ascitic or pleural fluid did not reaccumulate during the 6½ months of survival. There was also notable subjective improvement 2 weeks after the last injection. Her appetite improved, and the patient felt stronger and more fit. She had no chest pain and was able to walk without dyspnea. Five months after discharge subacute intestinal obstruction due to progressive enlargement of the pelvic and abdominal masses developed, and her condition deteriorated rapidly to a cachectic state and death.

later she was readmitted to the hospital because of weight loss, anorexia, weakness and recurrent ascites. The rapid reaccumulation of ascitic fluid required paracentesis at intervals of 2 or 3 weeks. On each occasion 2 or 3 liters of serous fluid was obtained. A left-sided pleural effusion productive of 650-1300 ml. of straw-colored fluid also developed at intervals of 2 or 3 weeks. Tumor cells were not demonstrable in the sediments.

Examination showed multiple, large, irregular intra-abdominal and pelvic masses that had resulted in partial intestinal obstruction with crampy abdominal pain, disten-

TABLE 2. *Types of Tumors and Effect of Administration of Hemisulfur Mustard.*

CASE NO.	PATIENT	ORGAN	PATHOLOGICAL DIAGNOSIS*	SITE OF METASTASES	NO. OF INJECTIONS	TOTAL DOSE
						(mg.)
1	J.S.†	Ovary	Undifferentiated carcinoma	Peritoneum	3	1140
2	E.G.	Ovary	Adenocarcinoma	Peritoneum	3	770
3	B.R.†	Ovary	Papillary carcinoma	Peritoneum & pleura	3	600
4	E.W.	Ovary	Adenocarcinoma	Peritoneum	5	800
5	E.Gr.	Ovary	Adenocarcinoma	Peritoneum & liver	2	500
6	F.L.	Ovary	Undifferentiated carcinoma	Peritoneum	2	400
7	H.B.	Ovary	Adenocarcinoma	Peritoneum	2	400
8§	B.D.†	Ovary	Papillary cystadenocarcinoma	Peritoneum & liver	4 3	950 700
9	H.C.†	Ovary	Adenoacanthoma	Peritoneum & lungs	3	600
10	E.C.†	Ovary	Papillary carcinoma	Peritoneum	3	600
11	B.L.†	Ovary	Adenocarcinoma	Peritoneum	3	800
12	E.S.	Ovary	Adenocarcinoma	Peritoneum	4	900
13	L.B.	Ovary	Adenocarcinoma	Peritoneum & liver	3	700
14	I.S.	Ovary	Papillary carcinoma	Peritoneum, lungs & pleura	1	200
15	E.G.†	Stomach	Adenocarcinoma	Peritoneum, lungs, diaphragm & ovaries	3	750
16	J.B.	Stomach	Adenocarcinoma	Peritoneum, pleura & ovaries	3	600
17	E.B.	Stomach	Undifferentiated carcinoma	Peritoneum	2	500
18§	D.L.	Colon	Adenocarcinoma	Peritoneum	3 3	450 600
19	S.C.	Colon	Adenocarcinoma	Peritoneum	2	500
20	M.L.	Colon	Adenocarcinoma	Peritoneum, liver & lungs	3	800
21§	J.B.†	Uterus	Mixed mesodermal tumor	Peritoneum	3 3	800 700
22	S.J.	Primary lesion unknown	Abdominal carcinoma	Peritoneum & liver	3	700
23	M.G.	Primary lesion unknown	Abdominal papiliary adenocarcinoma	Peritoneum & iliac bone	3	575
24	M.B.	Lymphoma	Giant-follicle lymphoma	Lymph nodes	3	700
25	A.B.	Lymphoma	Lymphosarcoma	Lymph nodes & cerebrum	3	320
26	R.M.	Lymphoma	Hodgkin's lymphoma	Lungs & lymph nodes	4	325
27	B.L.	Lymphoma	Reticulum-cell lymphoma	Lymph nodes (abdominal carcinoma)	4	850
28	B.S.	Lymphoma	Reticulum-cell lymphoma	Lymph nodes, skull, skin & lungs	3	400
29	A.B.†	Kidney	Clear-cell carcinoma	Peritoneum	3	600
30	S.K.	Kidney	Malignant adenocarcinoma	Peritoneum & pleura	3	600

*We are indebted to Dr. Leopold Reiner, Department of Pathology, for pathological diagnoses.
†Case reports given in text.
‡Patient also had intestinal obstruction due to neoplastic invasion & torsion of loops of small bowel.
§Two courses of hemisulfur mustard.
¶No ascites before therapy.
‖Good response to radiation.

CASE 3. A 47-year-old woman had a subtotal hysterectomy and bilateral salpingo-oöphorectomy for papillary alveolar carcinoma of the ovaries with metastases to the peritoneum and omentum. Postoperatively she received x-ray therapy to the abdomen and pelvis. Nine months

tion and obstipation. Hemisulfur mustard (600 mg.) was given in 2 equally divided doses on alternate days. The only reaction was nausea and vomiting. A month later the patient was greatly improved. Intestinal obstruction was relieved, and the abdomen was soft and flat and she had

daily bowel movements. There was also moderate shrinkage of the intra-abdominal masses. Her appetite improved, and she gained 9.1 kg. (20 pounds) in weight and felt much stronger. Ascitic fluid did not reaccumulate for 4 months after the last injection. Two months later she began to deteriorate rapidly and died in cachexia 7 months after administration of hemisulfur mustard.

CASE 8. A 41-year-old woman, 5 months before admission, had had bilateral salpingo-oöphorectomy for bilateral ovarian papillary cystadenocarcinoma with multiple peritoneal implants followed by x-ray therapy to the pelvis. She was admitted to the hospital because of recurrent ascites and partial obstruction of the lower intestine. She appeared cachectic. The abdomen was distended with fluid (3 liters). There were an enlarged nodular liver and multiple firm, irregular, fixed, nodular masses in the pelvis and abdomen. She received 4 injections of hemisulfur mustard (950 mg.) in the course of 7 days. After the last injection a transient (4-day) dysarthria, diplopia, tremor and dizziness developed. After therapy she gained weight and strength. There was no evidence of reaccumulation of ascitic fluid. The palpable abdominal and pelvic masses became much smaller. She had no further abdominal pain, nausea or vomiting. Four months later, however, she was readmitted to the hospital with dyspnea, abdominal cramps, vomiting and constipation. She had bilateral pleural effusion and incomplete small-bowel obstruction. Repeated thoracentesis yielded 0.5 to 1 liter of serosanguineous fluid from each pleural cavity. No tumor cells could be identified in the sediment. A second course of hemisulfur mustard (700 mg.) was administered in divided doses on alternate days.

TABLE 2 *(Concluded).*

CASE NO.	SUPPRESSION OF ASCITES	DISAPPEARANCE OF CARCINOMA CELLS FROM ASCITIC FLUID	GENERAL PALLIATION	DURATION OF LIFE	TOXIC REACTION BESIDES NAUSEA, VOMITING & MALAISE	BENEFICIAL EFFECT
				mo.		
1	Yes	Yes	Yes	6½	None	Yes
2	Yes	Yes	No	9	Causalgia	Yes
3	Yes	None initially	Yes	7	None	Yes
4	None	No	No	2	None	No
5	Yes	Yes	Yes	7	Convulsions	Yes
6	No	No	No	6	Shock‡	No
7	No	——	No	¼	Sudden death (? pulmonary embolism)	No
8§	Yes No	None initially	Yes No	8	Dizziness, tremor, diplopia & dysarthria None	Yes No
9	Yes	Yes	Yes	11	None	Yes
10	Yes	None initially	Yes	8	None	Yes
11	Yes	Yes	Yes	3	None	Yes
12	Yes	Yes	Yes	3	None	Yes
13	No	No	No	6	None	No
14	No	No	No	1½	None	No
15	Yes	Yes	Yes	7	None	Yes
16	¶	Yes	No	5	Prostration	Yes
17	No	Not done	No	½	None	No
18§	No	None initially	No	6	None	No
19	No	None initially	No	6	None	No
20	No	No	No	4	None	No
21§	Yes No	Yes	Yes No	28 2	None	Yes Yes
22	No	No	No	1	None	No
23	¶	None initially	No	2	None	No
24	¶	——	0	‖	None	No
25	¶	——	0	1	None	No
26	¶	——	0	¾	None	No
27	¶	——	0	2	None	No
28	¶	——	0	1	None	No
29	Yes	None initially	Yes	6	Convulsions	Yes
30	0	——	0	6	None	No

*We are indebted to Dr. Leopold Reiner, Department of Pathology, for pathological diagnoses.
†Case reports given in text.
‡Patient also had intestinal obstruction due to neoplastic invasion & torsion of loops of small bowel.
§Two courses of hemisulfur mustard.
¶No ascites before therapy.
‖Good response to radiation.

After each injection transient nausea, vomiting, malaise and tremor developed. The intestinal obstruction was relieved. Ascitic fluid did not reaccumulate for 4 months of survival after the 2d course of therapy. Terminally, she showed recurrent pleural effusion and progressive enlargement of abdominal masses, weakness and cachexia.

CASE 9. A 74-year-old woman was admitted to the hospital 1 year after a panhysterectomy for adenoacanthoma of the uterus. At operation extensive intra-abdominal metastases had been encountered. Eight months before admission weight loss, anemia and ascites developed. Fluid

FIGURE 1. *Biopsy Taken at the First Operation in Case 21 (S51-3685), Showing Solid Nests of Carcinoma in the Omentum (Hematoxylin and Eosin Stain X260). The fibrous septa are infiltrated with lymphocytes.*

reaccumulated at such a rate as to require paracentesis productive of 3 to 5 liters of serosanguineous fluid at 3-week intervals. The sediment regularly contained tumor cells. On admission she was cachectic, dehydrated and anemic. She had ascites, a large irregular mass in the left upper quadrant, a smaller mass in the right lower quadrant and a 3d palpable mass in the pelvis. There was also evidence of pulmonary metastases. Paracentesis yielded 2600 ml. of bloody fluid. She was given 600 mg. of hemisulfur mustard in 3 equally divided doses over an 8-day period. Her reaction included nausea, vomiting, weakness and tremor. Ascitic fluid did not reaccumulate for 5 months. Thereafter, she deteriorated steadily, dying 2 months later.

CASE 10. Operation on this 61-year-old woman disclosed papillary carcinoma of both ovaries, with extensive intraperitoneal metastases. A bilateral oöphorectomy was performed, and postoperatively she received deep radiation therapy to pelvis and abdomen, with only transient palliation. Five months later she was readmitted to the hospital because of abdominal pain, discomfort and general disability. She also complained of intractable pain in the back and shoulders. Her symptoms were refractory to testosterone and estrogens. Extensive metastases had occurred to the lumbar spine. Large abdominal masses, with progressive abdominal distention due to ascites, were apparent. She required paracentesis at intervals of 2 or 3 weeks, each productive of 2 to 5 liters of serosanguineous fluid. Tumor cells were not demonstrable in the sediment. She received hemisulfur mustard (600 mg.) in 3 equally divided doses over a period of 10 days. Each injection resulted in transient nausea, vomiting and malaise. She continued to complain of severe pain in the abdomen, back and left shoulder. This required large amounts of narcotics for palliation, which precipitated confusion and disorientation, and a paranoid tendency developed. Sedation was discontinued, and she received intensive psychotherapy. Her mental state showed considerable clearing although she still harbored some paranoid ideas. There was substantial shrinkage of the abdominal masses, but x-ray examination of the lumbar spine showed no change. The pain was much less severe, and she improved clinically. Ascitic fluid did not reaccumulate during the 8 months of survival after hemisulfur mustard. Terminally, the abdomen became distended with numerous large masses; nausea and vomiting developed, and she became progressively weaker and died in cachexia.

CASE 11. A 43-year-old woman had a right-sided salpingo-oöphorectomy for adenocarcinoma of the ovary with extension to the left adnexa, peritoneum and omentum. This was followed by x-ray therapy to the pelvis and abdomen, without substantial improvement. She continued to deteriorate, with weight loss, malaise, weakness, abdominal and chest pain and dyspnea due to bilateral pleural effusion and ascites. She required paracentesis and thoracentesis at intervals of 2 or 3 weeks. Each tap was productive of 1 to 5 liters of bloody effusion. Tumor cells were demonstrable in the sediment of the ascitic fluid only. On admission she appeared cachectic and dyspneic. She had an enlarged liver, multiple large, nodular pelvic and intra-

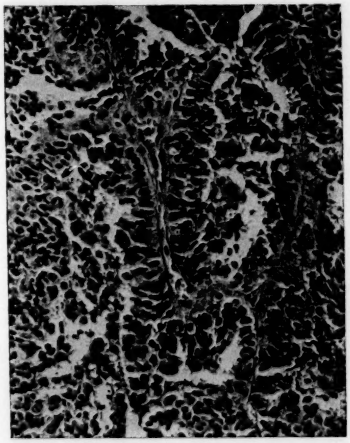


FIGURE 2. *Biopsy Taken at Curettage of the Uterus in Case 21 (S53-1109), showing the Carcinomatous Portion of a Mixed Mesodermal Tumor of the Uterus — Carcinosarcoma (Hematoxylin and Eosin Stain X260).*

abdominal masses, bilateral pleural effusion and ascites. She received 800 mg. of hemisulfur mustard in all on alternate days. After the 2d and 3d injections vomiting, malaise and tremor developed and persisted for 10 days. Thereafter, ascitic fluid did not reaccumulate. She had recurrent pleural effusion but was able to get along without thoracentesis. She survived for 7 months after the administration of hemisulfur mustard and died in cachexia with progressive enlargement of abdominal and pulmonary metastases and progressive intestinal obstruction.

CASE 15. A 56-year-old female with weakness, weight loss, anorexia and painless abdominal swelling was found to have scirrhous carcinoma of the stomach (linitis plastica), with extensive metastases to the omentum, peritoneum and

both ovaries (Krukenberg tumors). Bilateral oöphorectomy was performed. Shortly afterward she received a course of injections of nitrogen mustard without improvement. She continued to lose weight, and ascitic fluid reaccumulated, requiring paracentesis at 2-week intervals, each productive of 2 to 5 liters of straw-colored fluid. On admission 6 months after the initial operation she appeared cachectic and had a large, nodular liver, multiple large, nodular abdominal masses and ascites. She received hemisulfur mustard (750 mg.) in 3 injections over a 12-day period. After the 2d and 3d injection she had vomiting, malaise, tremors and tinnitus. Thereafter, she showed considerable improvement. She felt stronger and more fit. Ascitic fluid no longer accumulated, and the palpable abdominal masses decreased in size. This improvement was of short duration (5 months). Thereafter, she showed recurrent ascites, pleural effusion, progressive weight loss, weakness and cachexia and she died within 2 months.

Case 21.* A 70-year-old woman had a painless swelling of the abdomen. On admission her abdomen was swollen, and a vaguely palpable mass in the upper abdomen was identified. Operation showed extensive nodular involvement of the omentum creating 1 large palpable mass, and the peritoneal structures were studded with nodules of carcinoma but no primary source was disclosed. The liver was free of metastases, and the pelvic structures as well as the entire gastrointestinal tract were explored for a palpable mass but none was found. The pancreas and gall

Figure 3. *Biopsy from the Omentum Taken at the Second Laparotomy in Case 21 (S53-1190), Showing a Poorly Differentiated Adenocarcinoma (Hematoxylin and Eosin Stain X260).*

There are scattered psammoma bodies throughout the field. The stroma contains lymphocytes.

bladder also appeared normal. There were 2 liters of peritoneal fluid. The sediment contained carcinoma cells. A biopsy (Fig. 1) was taken from the peritoneum and omentum, and the abdomen was closed. She received hemisulfur mustard (700 mg.) in 3 doses, with a moderate reaction of nausea, vomiting and malaise. There was progressive and remarkable improvement. She gained weight and strength. The palpable abdominal mass disappeared, and she had no further ascites. She was able to carry out her usual daily duties without discomfort or symptoms of any sort.

She remained remarkably well for the subsequent 16 months, when she was readmitted to the hospital with vaginal bleeding. Physical examination was negative. Dilatation and curettage yielded neoplastic tissue (Fig. 2). A panhysterectomy and bilateral salpingo-oöphorectomy were performed for a mixed mesodermal tumor of the endometrium. Exploration at laparotomy gave no evidence of the intra-abdominal tumor that had been so widespread and obvious at the previous operation. The peritoneum was smooth and glistening. There was no free fluid and no obvious carcinomatous implants in the omentum or in any of the organs, including the gastrointestinal tract, liver, spleen and peritoneal surface. The omentum was no longer a large palpable mass but soft and normal to gross examination. A large piece was taken for microscopical examination. A small ventral hernia was found and repaired, and the peritoneum of the hernial sac was taken for examination, because of its rather cobblestoned type of feel, although no grossly neoplastic tissue could be identified. Small nests of papillary carcinoma cells, found in all tissue removed (Fig. 3), were similar to the lesion that had been biopsied at a previous operation. Recovery was uneventful, and she was discharged relatively well. She was readmitted to the hospital 6 months later for the 3d time with acute cholecystitis. A cholecystectomy was performed, and at operation again there was no ascites and no gross evidence of carcinoma. A biopsy of the omentum, however, revealed adenocarcinoma (Fig. 4). The postoperative convalescence was rapid and uneventful.

Figure 4. *Biopsy Taken at the Third Laparotomy in Case 21 (S53-3186), Showing a Poorly Differentiated Adenocarcinoma in the Omentum (Hematoxylin and Eosin Stain X260).*

Note the fibrosis of the stroma.

Four months later (29 months after the initial course of hemisulfur mustard) pain in the upper abdomen, anorexia and constipation developed. On admission she had obvious recurrence of the intra-abdominal neoplastic process, with multiple abdominal masses and ascites. She received a 2d course of hemisulfur mustard (700 mg.) without response and died 6 weeks later.

Case 29. Laparotomy on this 64-year-old man revealed a large, inoperable clear-cell carcinoma of the kidney, with extensive retroperitoneal metastases. Fifteen months later he was readmitted to the hospital with massive recurrent ascites, weakness and pain in the back. Paracentesis every 6 or 7 days yielded 4 to 5 liters of straw-colored fluid. The sediment did not contain tumor cells. He received hemisulfur mustard (600 mg.) in 3 injections over a 7-day period. After the 3d injection he became disoriented, with a tremor of the extremities, and had 2 convulsive seizures. Six weeks later there was marked improvement. His appetite was excellent. He gained 9.1 kg. (20 pounds) in weight and

*We are indebted to Drs. Samuel Gargill and Jacob Fine for referral of this patient.

felt much stronger and more fit. He had no further pain in the abdomen and back and felt well and strong. The abdomen was soft and flat, without evidence of recurrent ascites. This improvement lasted for 3 months. Thereafter he had recurrent ascites, weight loss and progressive cachexia. He died 6 months after the initial treatment.

Discussion

Hemisulfur mustard is a lipid-soluble, rather poorly water-soluble, unstable vesicant related to the much more toxic mustard gas, *bis* (beta-chlorethyl) sulfide. When this agent was found to be palliative, by temporary suppression of ascites in patients with peritoneal carcinomatosis, it was considered worth while to explore further the usefulness of a mustard agent that had the apparently unique property of being more effective against carcinoma than lymphoma. Toxicity associated with the therapy consisted of nausea, vomiting, malaise and tremor. Neurotoxicity could be suppressed by the use of Dilantin and barbiturates. The local reactions due to the irritant and vesicant properties of hemisulfur mustard could be avoided by administration of the drug into a large vein (superior vena cava). No hematopoietic toxicity commonly associated with nitrogen mustard therapy as well as other alkylating agents was encountered with hemisulfur mustard.

The best results were achieved in 9 patients with ovarian carcinoma and 1 patient with a mixed mesodermal tumor of the endometrium and peritoneal carcinomatosis (of twenty-nine months' duration). The disease in all these cases was far advanced, and all other measures had become ineffective. Even more effective palliation might be produced in a larger percentage of patients with inoperable cancer of ovarian or uterine origin if the drug could be given somewhat earlier in the course of the disease.

No specific cytotoxic effect on tumor cells was demonstrable by microscopical examination of the tissues removed surgically or at autopsy. Because post-mortem study was performed long after treatment, it is not surprising that there was no cytologic evidence of damage to tumor cells present at that stage that could be directly attributed to previously administered hemisulfur mustard. The only evidence of cell damage was that suggested by disappearance of metastatic masses by direct gross inspection in 1 patient, and shrinkage of palpable tumor masses in other patients. However, in 1 patient in this group, who showed a striking remission, as well as in 2 patients previously described, there was evidence of a fibrotic peritoneal reaction in some places about metastatic nests of tumor in the peritoneum and omentum. Fibrosis per se was not extensive enough, in our opinion, to explain the palliation observed.

Summary

A preparation of 2-chloro-2'-hydroxydiethyl sulfide (hemisulfur mustard) was administered to 30 patients with inoperable cancer. Many of these patients had become refractory to radiation or other therapeutic measures.

The toxic reactions seen after treatment consisted of nausea, vomiting, malaise and tremor. Of the 30 patients treated 14 were temporarily benefited. The best results were achieved in patients with ovarian carcinoma and peritoneal carcinomatosis and in 1 patient with a mixed mesodermal tumor of the endometrium. Palliation consisted of decreased formation of ascites, decrease in size of tumor masses, decrease in pain and increase in appetite, strength and sense of well-being. The longest remission of symptoms observed in 1 patient was twenty-nine months.

CLINICAL DIAGNOSIS OF AORTIC-VALVE DISEASE*

Lieutenant Richard Gorlin, (MC) USNR,† and Robert B. Case, M.D.‡

PORTSMOUTH, VIRGINIA

THE surgical correction of aortic stenosis[1] differs so much from that for aortic insufficiency that it is incumbent upon the physician accurately to assess the relative importance of each valvular lesion. In addition, because of the attendant risks of surgery and the peculiar precipitous natural history of aortic-valve disease,[2] accurate determination of severity of the valvular lesion before the onset of frank congestive heart failure is essential. The diagnosis of the presence of pure aortic stenosis or isolated insufficiency is straightforward. When the two lesions are combined, however, clinical evaluation becomes more complex. Also, in contradistinction to mitral-valve disease,[3] the lesions of the aortic valve may coexist with equal severity.[4]

Many excellent papers have been written on this subject, but few have demonstrated how the clinician with presently available bedside methods may detect severe and potentially operable degrees of the disease especially when stenosis and insufficiency

*From the Cardiopulmonary Function Laboratory, United States Naval Hospital.

The opinions or assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the Navy Department or of the naval service at large.

†Officer-in-charge, Cardiopulmonary Function Laboratory, United States Naval Hospital; present address, Peter Bent Brigham Hospital, Boston.

‡Senior assistant surgeon, United States Public Health Service.

exist together. We have correlated available anatomic findings and physiologic data from cardiac catheterization with the clinical observations in a group of over 100 cases, 50 of which have been reported elsewhere.[5] Conclusions regarding both clinical and physiologic data of diagnostic importance have been modified and reinforced by the writings of Mitchell et al.,[6] Kumpe and Bean[7] and Goldberg, Bakst and Bailey.[8]

Differential Diagnosis

Symptoms

The only symptoms that may be of diagnostic help are an unusual awareness of the heart beat, with throbbing and even pain over the large arteries,[9] and attacks of sweating, flushing and tachycardia,[10] both of which occur in aortic insufficiency. Generally, however, symptomatology is of little help. Both lesions may exist in severe form for many years[6,7] without any symptomatology whatever. Angina pectoris, syncope, dyspnea, orthopnea and so forth — symptoms of excessive work of the left ventricle, insufficient cardiac output or left-sided heart failure — appear with practically the same frequency in both stenosis and insufficiency.[6] Although the basic hemodynamics differ in these two valvular lesions, the resulting inadequacies in coronary, cerebral and peripheral blood flow and increases in pulmonary venous pressure are quite similar in both.[4,8] Historically, then, the symptoms named above are of no value in differential diagnosis.

Palpation of Carotid Pulse

Palpation of the carotid pulse is of inestimable help in indicating which type of aortic-valve lesion predominates, and affords considerably more information than palpation at any other site. In pure stenosis the carotid pulse is normal to decreased in volume, has a delayed systolic peak or a plateau quality, and almost always a rough systolic thrill may be felt. The coarseness of this thrill should be emphasized. The thrill is best felt in the sitting position, is often more readily detected by palpation of the left common carotid artery and may be enhanced by expiration.

When there is significant regurgitation as well as stenosis, the carotid pulse will be fuller and quicker to the touch, will assume both a bisferious (twin-peaked) quality in systole and a collapsing quality in diastole (Fig. 1). Palpation will usually reveal a fine systolic purr, frequently in addition to the coarse systolic thrill of stenosis. The bisferious pulse and the purr in insufficiency depend on rapid ejection of a large volume of blood from the heart, and are rarely felt in pure stenosis unless the cardiac output is increased at the time of the examination. These two signs are not specific for insufficiency, however, and may be present whenever stroke output is increased as in pregnancy[11] or thyrotoxicosis. The patient may well have signs of tight stenosis, but the presence of a bisferious pulse or soft systolic purr indicates that there is also a large degree of insufficiency. A small carotid-pulse volume almost always means a low cardiac ejection per beat and hence is seen with severe stenosis. A large-volume ejection from the heart with aortic insufficiency initiates a forceful carotid and also peripheral pulse wave (Fig. 1) even though the actual amount of blood delivered to the tissues may be as low as in severe stenosis. With systemic atherosclerosis these findings become less meaningful.

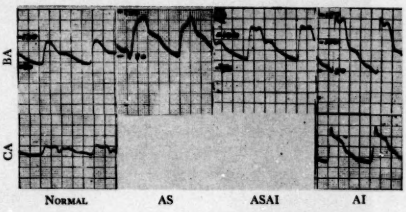


FIGURE 1. *Arterial Pressure Pulses in Disease of the Aortic Valve.*

BA=*brachial artery (direct recording).*

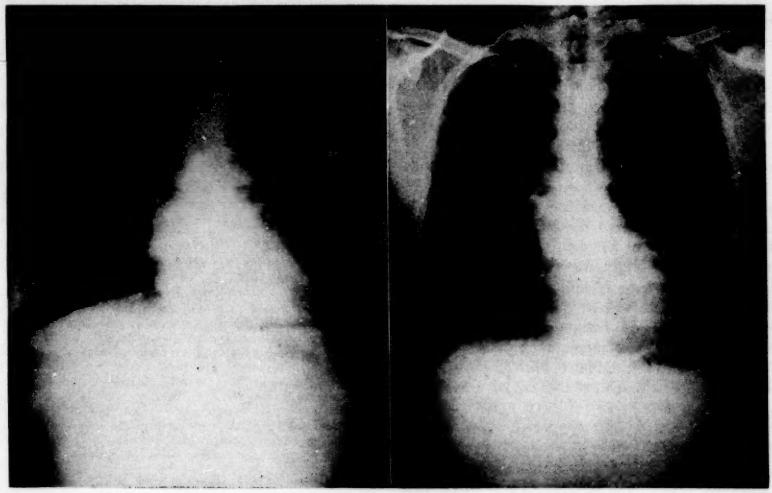
CA=*carotid artery (tambour recording). The normal brachial and carotid curves are seen on the left. The second curve illustrates the anacrotic notch, delayed systolic upstroke, long period of total systole and high dicrotic notch seen in aortic stenosis. The third curve shows the bisferious pattern (twin peak) in systole, the long systole and the intermediate pulse pressure seen in combined stenosis and insufficiency. The fourth curve shows the same bisferiens, but greater spiking, wider pulse pressure and lower diastolic pressure of isolated aortic insufficiency. The carotid wave emphasizes the easily palpable systolic thrust.*

Examination of the Heart

Examination of the heart itself may afford less information of diagnostic value than one would at first anticipate. There are, however, several minor differences between the two lesions that when combined have significance. Despite the well known muscular hypertrophy the heart size often shows little deviation from the normal in aortic stenosis[6] until the final stages of failure. In isolated insufficiency the heart enlarges at an early stage in the disease; therefore, when insufficiency is added to stenosis, clinically detectable cardiac enlargement usually denotes the presence of significant valvular insufficiency. Similarly, although the apical impulse may be forceful in aortic stenosis, the addition of insufficiency further accentuates this sign. In addition the apical impulse in insufficiency is more diffuse and rolling, and may be followed by a diastolic shock.

One of the most misleading and yet most valuable signs in aortic disease is the quality of the murmur. It must be remembered that the intensity of the murmur is not only a function of valve size and shape but also closely correlated with the velocity of blood flow through it. Consequently, the usually rough systolic

murmur may be very faint (and sometimes absent) in isolated severe aortic stenosis[12] if a low cardiac output accompanies this lesion. Likewise, the detection of large-volume ejection with insufficiency, as denoted by an overactive carotid pulse, would make the presence of only a faint systolic murmur over the base of the heart synonymous with insignificant stenosis. Any fixed valvular deformity will result in the coarse, harsh murmur classically associated with aortic stenosis. Unfortunately, this quality bears no necessary relation to the severity of the anatomic stenosis. Similarly, the intensity of the diastolic murmur of insufficiency has no definite relation to the degree of regurgitation present.[13]



A B

FIGURE 2. *Roentgenograms in Aortic-Valve Disease.*
A=*predominant stenosis: enlargement of the ascending aorta to the right, with a small aortic knob.*
B=*predominant insufficiency: generalized dilatation of the ascending portion and arch of the aorta.*

Close attention to the aortic second sound sometimes yields information of value in the differential diagnosis. A decreased aortic sound is usually indicative of gross deformity with poor valve mobility but does not necessarily mean predominant stenosis. In fact, a decreased second sound may be heard even though there is predominant insufficiency. The finding may be further confused by the presence of a loud, widely transmitted pulmonic second sound, which may be mistakenly interpreted at the aortic area for a normal second sound.

X-Ray and Fluoroscopic Study

X-ray and fluoroscopic examination may help in a number of ways in differential diagnosis. In the first place any prominence of the silhouette of the left ventricle in the left anterior oblique view may be objectively evaluated. Secondly, in predominant aortic stenosis, there is usually poststenotic dilatation of the first portion of the aorta (Fig. 2*A*). In predominant aortic insufficiency, whether or not stenosis is associated, the aortic knob, as well as the ascending aorta, is prominent (Fig. 2*B*). In aortic insufficiency, fluoroscopy should confirm increased cardiac ejection of blood by revealing a rocking heart beat. Valvular calcification is usually associated with marked valvular deformity but by no means indicates stenosis as the predominant lesion and therefore has little value in differential diagnosis.[5]

Hemodynamic Studies

Hemodynamic studies to date have not been as revealing in differential diagnosis as was anticipated. It is well known that aortic stenosis characteristically results in a narrow pulse pressure whereas pure aortic insufficiency results in a wide pulse pressure with low mean, dicrotic and diastolic blood pressures.[8] When present together one aortic lesion tends to neutralize the characteristic pressure pulse of the other.[4] The directly recorded arterial pulse may reveal suggestive changes in mean and dicrotic pressure levels not otherwise noted by clinical methods. In addition the phenomenon of anacrotism in predominant stenosis that cannot always be palpated may be shown. Un-

fortunately, further refinements, including measurements of pressure changes in relation to time and the various periods of systole, do not always help in the individual case. Evaluation of the central aortic pulse and its propagation to the periphery is now under study by Roshe[14] and may eventually be rewarding. Catheterization of the right side of the heart is of help only in determining the functional status of the left side.[4,8] On the other hand, catheterization of the left side[15,16] permits direct measurement of the valvular pressure gradients. Technics are currently being developed for assessing the amount of regurgitation in aortic insufficiency. With these advances it may be possible to calculate the true valve area in doubtful cases.

Confusing Signs of Combined Stenosis and Insufficiency

It has become obvious from the foregoing discussion that when stenosis and insufficiency are combined some of the signs of one intensify signs of the other, some are merely superimposed, and others may cancel. In this fashion, aortic insufficiency intensifies all the signs of aortic stenosis that are dependent on velocity of blood flow — for example, the intensity of cardiac thrills and murmurs. The signs of increased cardiac ejection that go with aortic insufficiency — the carotid pulse and the soft arterial thrills, the rocking beat and so forth — are on the other hand merely superimposed upon those of stenosis. Finally, the blood-pressure findings in either disease nullify those in the other, depending on individual severity of the lesions involved. Therefore, signs due to superimposition of insufficiency upon stenosis have the greatest value in differential diagnosis. Carotid and cardiac activity and the nature of the thrill stand out as most useful signs.

Determination of Severity of the Individual Lesion

Physiologic studies combined with anatomic observations have indicated that in the absence of regurgitation a severe degree of pure stenosis is represented by a cross-sectional area of 0.5 sq. cm.[4] This area is approximately 15 per cent of the normal orifice size. At this stenosis systolic pressures in the left ventricle approach and exceed 200 mm. of mercury; cardiac output is depressed, and coronary blood flow is relatively fixed. In aortic insufficiency whenever aortic-valve closure leaves a defect of 0.3 sq. cm. or larger, significant regurgitation occurs with leaks of blood equal to and probably up to three times the useful or systemic cardiac output. When aortic insufficiency is associated with stenosis the aortic-valve flow in systole is naturally increased; this results in an increased pressure gradient across the aortic valve and the accentuation of the physiologic severity of any existing anatomic stenosis.[4]

Other workers have shown that aortic stenosis or insufficiency may be severe in degree without the presence of any symptoms whatever.[6,7] This is confirmed by our own studies.[5] When, however, a patient with the diagnosis of aortic stenosis or insufficiency has frank exertional dyspnea or the presence of syncope or dizzy spells, the lesion usually is severe.[5-7] Angina pectoris by itself has no diagnostic significance when the age of the patient is advanced, since such a symptom may be caused by coronary atherosclerosis as well as by severe stenosis or insufficiency.[17] When congestive heart failure has developed, with recurrent bouts of pulmonary edema and dyspnea, and especially when there is right-sided failure in addition, the myocardium has become involved, and the disease is approaching its last stages.[4] Aortic stenosis, if present, has usually been severe for many years.

There are only a few physical signs that in themselves denote the severity of the underlying valvular lesion. A decreased aortic second sound in the absence of associated insufficiency usually means severe stenosis although the converse is not true. Cardiac enlargement is often not striking, nor is the apex impulse unusual in aortic stenosis except possibly to be more forceful than normal. The intensity of the murmur likewise is of no help. If, however, the murmur *decreases* in intensity over the course of time this probably signifies that cardiac output is decreased, severe congestive heart failure imminent and stenosis severe. Finding the characteristic pulse in the carotid artery is helpful especially if it is decreased in volume and vigor.

Short of the characteristic blood-pressure findings, the vigor and volume of cardiac ejection, as signified by carotid and cardiac signs of hyperactivity, are the only bedside clues to severity in pure insufficiency. When insufficiency and stenosis are combined, unfortunately, the anatomic severity of stenosis cannot be diagnosed by means of physical signs; the degree of aortic insufficiency may be judged, however, as mentioned above.

It is almost essential that the electrocardiogram demonstrate left-ventricle hypertrophy, left-bundle-branch block or delayed *intrinsicoid* deflection over the left ventricle. This was observed in 85 per cent of two series of patients with severe stenosis as determined anatomically or physiologically.[5,6] The combination of hypertrophy of the left ventricle in a normal-sized heart suggested pure, tight stenosis. On the other hand, it is well to point out that though 15 per cent of patients show no electrocardiographic abnormality, stenosis may be severe.[18]

Certain functional hemodynamic changes occurring in the clinical course of the disease may offer valuable clues to severity. In aortic insufficiency the pulse pressure and diastolic pressure change with the onset of congestive heart failure, and this may antedate clear-cut symptoms. The systolic blood pressure tends to fall, and the very low diastolic blood pressure tends

to rise as the vasodilatation of insufficiency gives way to the low cardiac output and vasoconstriction of heart failure.[19] As a result the pulse pressure decreases markedly from former values. There are few warning signs of the onset of cardiac failure in aortic insufficiency, and classically this onset may be abrupt. Such a change in pressure may serve as the first clue to impending cardiac failure.

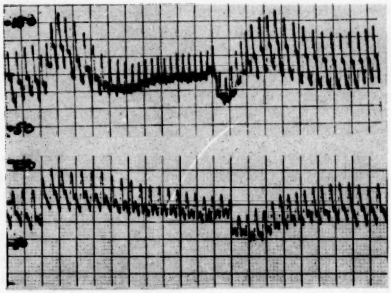


FIGURE 3. *Arterial Blood-Pressure Recordings during Forced Airway Straining to 40 Mm. of Mercury (Valsalva Maneuver) in a Normal Person (Top Tracing) and an Asymptomatic Patient Adjudged by Electrocardiographic and Catheterization Studies to Have Severe Aortic Stenosis (Lower Tracing).*

Note the normal rapid fall in pressure immediately with onset of straining whereas in aortic stenosis the pressure remains unchanged for seven beats. This can be detected with a sphygmomanometer.

An abnormal blood-pressure response to the Valsalva maneuver in a patient with predominant aortic stenosis indicates that the stenosis is severe (0.5 sq. cm. or less if the lesion is pure).[20] The abnormal response is readily detected at the bedside by means of a sphygmomanometer.[21] During positive airway strain the blood pressure, instead of falling normally within a few beats, remains elevated or falls very slowly (Fig. 3). This pattern is characteristic of a flat or abnormal ventricular-function curve and is seen in severe aortic stenosis long before symptoms occur. This type of response does not occur in aortic insufficiency until frank failure supervenes.

Elaborate physiologic studies can make certain definite contributions in determining the degree of pure stenosis. Cardiac-catheterization studies have shown that patients with tight aortic stenosis, long before obvious heart failure has developed, will not increase their blood pressure, stroke output or left-ventricle stroke work above their resting value during exercise.[4] This unusual finding has not been seen with the milder degrees of stenosis, with aortic insufficiency or in patients with hypertensive heart failure short of the preterminal state. The newer technics utilizing puncture of the left atrium and catheterization of the left ventricle make it possible in selected problem cases to measure the pressure gradient across the aortic valve during systole[15] and to calculate the aortic-valve area.[16] With this information, a diagnosis of tight aortic stenosis may be made. In pure stenosis the valve gradient ranges from 35 to 150 mm. of mercury, depending mainly on cardiac output and heart rate at the time of observation.[4,16] When aortic insufficiency is combined, it is necessary to measure total aortic-valve flow. Recent studies utilizing the Korner–Shillingford method of analysis of indicator dilution curves[22] hold considerable promise in estimating both qualitatively and quantitatively the degree of valvular leak (and, therefore, valve area).[23]

CONCLUSIONS

Determination of predominance and severity of stenosis and insufficiency of the aortic valve when the two lesions are combined has assumed importance because of the imminence of corrective surgery.

The predominant lesion may be diagnosed at the bedside. Differentiation is best made possible by physical signs; history, cardiac catheterization and fluoroscopic and electrocardiographic studies make definite but minor contributions. The most helpful signs are those related to the degree of activity of the heart and arterial vessels.

The absence of symptoms does not preclude lack of severity of either valvular lesion. During this asymptomatic phase any decrease in the intensity of the murmur or in pulse pressure or change in the blood-pressure response to the Valsalva maneuver may serve as an early clue to the presence of severe aortic-valve disease. Hypertrophy of the left ventricle or a strain pattern by electrocardiogram is usually present when either lesion is severe.

We are indebted to Drs. M. B. Matthews and W. E. Medd and the members of the Department of Cardiology, St. Thomas' Hospital, London, for their invaluable contributions to this paper.

REFERENCES

1. *Henry Ford Hospital: International Symposium on Cardiovascular Surgery: Studies in physiology, diagnosis and techniques: Proceedings of the symposium held at the Hospital, Detroit, Michigan, March, 1955.* Edited by C. R. Lam. 543 pp. Philadelphia: Saunders, 1955.
2. Peacock, T. B. *On the Prognosis in Cases of Valvular Disease of the Heart.* 55 pp. London: Churchill, 1877.
3. Gorlin, R., Lewis, B. M., Haynes, F. W., and Dexter, L. Studies of circulatory dynamics at rest in mitral valvular regurgitation with and without stenosis. *Am. Heart J.* **43**:357-394, 1952.
4. Gorlin, R., McMillan, I. K., Medd, W. E., Matthews, M. B., and Daley, R. Dynamics of circulation in aortic valvular disease. *Am. J. Med.* **18**:855-870, 1955.
5. Matthews, M. B., Medd, W. E., and Gorlin, R. Aortic stenosis: clinical study. *Brit. M. J.* **2**:759-763, 1955.
6. Mitchell, A. M., Sackett, C. H., Hunzicker, W. J., and Levine, S. A. Clinical features of aortic stenosis. *Am. Heart J.* **48**:684-720, 1954.
7. Kumpe, C. W., and Bean, W. B. Aortic stenosis: study of clinical and pathological aspects of 107 proved cases. *Medicine* **27**:139-185, 1948.
8. Goldberg, H. A., Bakst, A. A., and Bailey, C. P. Dynamics of aortic valvular disease. *Am. Heart J.* **47**:527-559, 1954.
9. Harvey, W. P., Segal, J. P., Ari, R., and Hufnagel, C. Unusual clinical features associated with severe aortic insufficiency. *Circulation* **12**:719, 1955.
10. Lewis, T. Angina pectoris associated with high blood pressure and its relief by amyl nitrite: with note on Nothnagel's syndrome. *Heart* **15**:305-327, 1931.

11. Matthews, M. B. Personal communication.
12. Christian, H. A. *The Diagnosis and Treatment of Diseases of the Heart.* (Reprinted from *Oxford Monographs on Diagnosis and Treatment.*) 599 pp. New York: Oxford University Press, 1940.
13. Lewis, T. *Diseases of the Heart Described for Practitioners and Students.* Second edition. 297 pp. New York: Macmillan, 1937.
14. Roshe, J. Central and peripheral arterial pulses: quantitative study in dogs with normal and incompetent aortic valves. *Surgery* (in press).
15. Bjork, V. O., and Malmstrom, G. Diagnosis of aortic stenosis. *Am. Heart J.* **58**:303-307, 1955.
16. Goldberg, H., Dickens, J., Hayes, E., and Raber, G. Simultaneous catheterization of left and right sides of heart. *Circulation* **12**: 713, 1955.
17. Anderson, M. W., Kelsey, J. R., Jr., and Edwards, J. E. Clinical and pathological considerations in cases of calcific aortic stenosis. *J. A.M.A.* **149**:9-15, 1952.
18. Harvey, W. P. Personal communication.
19. Gorlin, R., and Goodale, W. T. Clinical significance of changing blood pressure in aortic insufficiency. *New Eng. J. Med.* **253**:77-79, 1955.
20. Gorlin, R., Knowles, J. H., and Storey, C. F. Valsalva maneuver as test of cardiac function: pathologic physiology and clinical significance. *Am. J. Med.* (in press).
21. Knowles, J. H., Gorlin, R., and Storey, C. F. Clinical test for pulmonary congestion with use of Valsalva maneuver. *J.A.M.A.* **160**:44-48, 1956.
22. Korner, P. I., and Shillingford, J. P. Quantitative estimation of valvular incompetence by dye dilution curves. *Clin. Sc.* **14**:553-573, 1955.
23. Novack, P., Schlant, R., Haynes, F. W., and Dexter, L. Personal communication.

SALT-LOSING NEPHRITIS*

Review and Report of a Case

ARTHUR H. LEVERE, M.D.,† AND LAURENCE G. WESSON, JR., M.D.‡

NEW YORK CITY

THE phenomenon of excessive loss of salt in the urine of patients with chronic Bright's disease has been known for many years. Peters and his coworkers,[1] in 1929, described patients with renal disease who had excessive excretion of chloride in the urine in spite of markedly decreased serum chloride concentrations. By giving large amounts of salt, they found it possible to maintain serum chloride at normal values. They suggested that in some cases of nephritis salt deprivation was dangerous and, indeed, recommended supplemental sodium chloride to prevent salt depletion.

In 1944 Thorn, Koepf and Clinton[2] first reported the clinical implications of salt loss when they described 2 cases of renal failure simulating adrenocortical insufficiency. Since 1944 12 additional case reports under the heading of "salt-losing nephritis" have been published.[3-9] Symptoms of asthenia, weakness, nausea, vomiting, anorexia, weight loss and muscle cramps were observed and considered to be due to excessive urinary loss of sodium chloride. To these particular cases of chronic renal disease, presenting a fairly distinctive clinical picture and with predominant signs and symptoms of salt depletion, Thorn gave the name "salt-losing nephritis." The present paper reports an additional case, briefly reviews the various salt-losing states and proposes criteria essential to establish the diagnosis of salt-losing nephritis, based upon published cases.

CASE REPORT

C.A., a 29-year-old married policeman, first entered Bellevue Hospital on January 17, 1954, complaining of weakness, nausea and vomiting of 5 weeks' duration. He was referred by a police-department physician because of an unexplained anemia.

He had apparently been in good health all his life. He recalled no unusual childhood diseases. He was in the Army from 1944 to 1946 and passed a police-department physical examination in 1952.

Five weeks before admission, he began to experience aching and cramps in his limbs, accompanied or soon followed by nausea and vomiting without hematemesis and usually while he was riding in vehicles. He also noticed weakness, fatigue, exertional dyspnea, increasing thirst and polyuria, and a loss of 2.3 kg. (5 pounds) in weight.

Physical examination showed a well developed, well nourished, slightly pale man who weighed 80.7 kg. (178 pounds). The heart, lungs and retinas were normal.

The blood pressure was 124/80. The temperature was 98.6°F., and the pulse 100 and regular.

Examination of the blood revealed a red-cell count of 3,300,000, with a hemoglobin of 11.5 gm. per 100 ml., and a white-cell count of 8600, with 78 per cent neutrophils. The sedimentation rate was 61 mm. per hour (Wintrobe method), and the hematocrit 29 per cent. The blood Mazzini reaction was negative. The nonprotein nitrogen was 180 mg., the creatinine 8.4 mg., the fasting blood sugar 121 mg., the calcium 7.0 mg., and the phosphorus 8.0 mg. per 100 ml. The total protein was 8.9 gm., with an albumin of 2.4 gm. and a globulin of 6.5 gm. per 100 ml. The sodium was 131 milliequiv., the potassium 6.6 milliequiv., and the carbon dioxide 16 milliequiv. per liter.

The specific gravity of the urine was 1.010, with an acid reaction and negative tests for protein and sugar. The sediment contained 1 or 2 white and red cells per high-power field and no casts. All subsequent urinalyses were similar. Cultures obtained showed no growth. The urine was negative for lead. Retrograde pyelography was normal. An intravenous phenolsulfonphthalein test revealed less than 5 per cent excretion in 15 minutes and less than 20 per cent in 2 hours. Paint and paint thinners, which the patient had used indoors 3 months before admission, were found to be free of halogenated hydrocarbons. X-ray films of the chest and a gastrointestinal series were normal.

His condition deteriorated rapidly although therapy for chronic renal disease had been instituted. An electrocardiogram on January 23 revealed prominent peaked T waves. The plasma potassium at this time was 7.6 milliequiv. per liter. He became lethargic and markedly nauseated and vomited. Sodium carboxylic acid exchange resin was given by high-colonic enema to reduce the elevated serum potassium. Glucose was administered intravenously. The blood pressure decreased to 100/60. The stool guaiac test became positive, and bleeding from the gums was observed. Hematologic study revealed normal bone marrow, a prothrombin time of 100 per cent, normal bleeding and clotting times, a platelet count of 305,000 and a normal reticulocyte count.

*From the Department of Medicine, Post-Graduate Medical School, New York University, and the Fourth Medical Division, Bellevue Hospital.

†Instructor in medicine, Post-Graduate Medical School, New York University; resident in medicine, University Hospital.

‡Associate professor of medicine, Department of Medicine, Post-Graduate Medical School, New York University; visiting physician, Bellevue Hospital.

Seven days after admission the creatinine had risen to 11.6 mg. per 100 ml.; the potassium was 5.9 milliequiv. (after use of the resin), and the sodium 123 milliequiv., and the chloride averaged 57 milliequiv. per liter. With a total 24-hour volume of 1.8 liters of urine the urinary chloride was 47 and the sodium 118 milliequiv. per liter. The hemoglobin fell to 7.5 gm. per 100 ml.

The patient appeared better after an infusion of isotonic saline solution given in an attempt to correct suspected dehydration. Because of this, and the evidence of increased urinary excretion of sodium concomitant with a high degree of renal insufficiency, it was suspected that he had a salt-losing type of renal dysfunction. He was placed on intravenous infusions of glucose and saline solution, together with milk and 9 gm. of salt tablets daily, and this was gradually changed to oral feeding with an extra 9 gm. of salt and 3 gm. of calcium lactate daily as he improved. The urinary volume varied between 1.5 and 3.8 liters daily. On February 3 the total 24-hour excretion of sodium was 234, and that of chloride 259 milliequiv. Six days later urinary sodium excretion attained 334 milliequiv. in twenty-four hours.

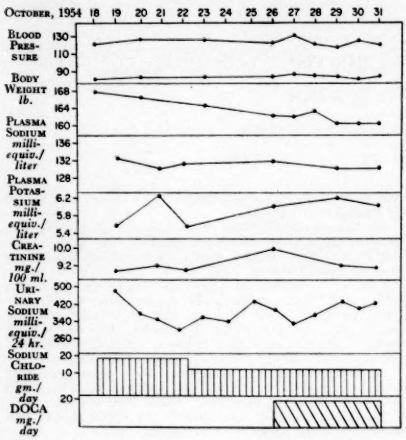


FIGURE 1. *Lack of Effect of Desoxycorticosterone Acetate in Oil (20 Mg., Intramuscularly, a Day) on Body Weight, Blood Pressure, Serum Electrolytes and Sodium Excretion in a Patient with "Salt-Losing Nephritis" on an Oral Intake of 16-20 Gm. of Sodium Chloride Daily.*

After February 6 the hospital course was uneventful. He was discharged on March 29, after 68 days in the hospital. At discharge the sodium was 134 milliequiv., the chloride 100 milliequiv., the potassium 5.0 milliequiv., and the carbon dioxide 21 milliequiv. per liter; the creatinine was 7.6 mg., the calcium 9.3 mg., the phosphorus 9.1 mg., and the blood urea nitrogen 130 mg. per 100 ml. The hemoglobin was 11 gm. per 100 ml.

After discharge he adhered to a low-protein diet with 6 to 10 gm. of supplementary salt and 3 gm. of calcium lactate daily, returning regularly to the out-patient clinic for follow-up examination. The 17-ketosteroid content of a 24-hour specimen of urine in September was 11.3 mg. He was readmitted to Bellevue Hospital for further metabolic studies in October, when the blood pressure was 120/80 and the pulse 92 per minute. He was alert and symptom free. Physical examination and x-ray study of the chest were negative. The hemoglobin was 11.5 gm. per 100 ml., the red-cell count 3,600,000, and the hematocrit 30 per cent. Six specimens of urine had a specific gravity of 1.006 to 1.009, with no protein or sugar; the sediment contained rare red and white cells, with no casts. The plasma sodium was 132 milliequiv., and the potassium 5.6 milliequiv. per liter; the calcium was 9.5 mg., the phosphorus 5.1 mg., and the creatinine 9.0 mg. per 100 ml. The total protein was 9.4 gm., with an albumin of 4.0 and a globulin of 5.4 gm. per 100 ml. Urinary 24-hour excretion of 17-ketosteroids was 13.2 mg., and that of 11-oxysteroids 1.0 mg.

While in the hospital he was placed on a 2400-calorie diet containing 30 gm. of protein and 16 gm. of supplementary salt daily, which, after 5 days, was decreased to 12 gm. of supplementary salt. The dietary salt content was calculated at 4 to 6 gm. per day. For 5 days during the 2d week 20 mg. of desoxycorticosterone acetate in oil was given intramuscularly each day. There was no significant change in blood or urinary findings. The blood pressure was stable; no edema developed, and the weight remained constant. The high rate of urinary excretion of sodium continued, varying between 350 and 400 milliequiv. per day (Fig. 1). The patient was discharged on October 31 on a diet containing 30 gm. of protein and 4-6 gm. of salt, with instructions to take 12 to 15 gm. of supplementary salt daily.

Since discharge he has been followed in the clinic and has remained on the prescribed diet, which has been supplemented recently by 3 gm. of sodium bicarbonate daily. Except for occasional calf and thigh cramps, he is relatively asymptomatic. He works 8 hours a day as a police clerk without excessive fatigue. He has remained normotensive; the heart and retinas are normal. No edema has developed, and the weight has been stationary. The hemoglobin is 11 gm. per 100 ml., and the red-cell count 3,500,000. The urine has never contained sulfosalicylic-acid-precipitable protein or significant sediment. The plasma sodium averages 130 milliequiv., the chloride 100 milliequiv., the carbon dioxide 18-22 milliequiv., and the potassium 5.0-6.5 milliequiv. per liter; the calcium is 8.5 mg., the blood urea nitrogen 120 mg., and the creatinine 7-8 mg. per 100 ml. Urinary volume averages 3.5 to 4 liters daily; fortnightly determinations of urinary sodium concentration average 120-124 and those of chloride 118 milliequiv. per liter, giving a daily sodium excretion of 430-490 milliequiv. and chloride excretion of 420-450 milliequiv.

Two needle biopsies were performed on the right kidney.* The 1st biopsy, taken on February 10, 1954, was described as follows:

> There is marked infiltration of the interstitial tissue by chronic inflammatory cells. Tubules show extensive degeneration. Some of the 6 glomeruli observed show irregular thickening of the basement membranes of the tufts and more marked thickening of the basement membrane of Bowman's capsule. There are some adhesions of tufts to Bowman's capsule, but no crescent formation or cellular proliferation. Other glomeruli appear normal. There is moderate thickening of arterioles.

The 2d biopsy, performed on April 13, 1956, was described as follows:

> The specimen includes about 15 glomeruli, 3 or 4 of which are completely hyalinized. The changes are similar to those noted in the 1st specimen. Thickening of the basement membranes is uniformly present, supporting glomerulonephritis as the most probable pathological diagnosis. The degree of membrane thickening, however, is too mild to permit this diagnosis to be established beyond doubt.

Discussion

Hyponatremia in the presence of a urine rich in sodium chloride is recognized in several conditions. In Addison's disease, a functional defect in renal tubular sodium chloride reabsorption due to deficient corticoid production results in salt wastage and signs and symptoms of dehydration, including an elevated

*Examined by Dr. Norman S. Cooper, of the Pathology Division, Bellevue Hospital, and the Department of Pathology, New York University College of Medicine.

blood urea nitrogen. Most of the symptoms respond to sodium chloride administration, and the tubular defect is specifically reversible by corticoid administration. Salt-losing nephritis has many features in common with Addison's disease. It differs principally in the circumstance that the defect in tubular sodium chloride reabsorption is organic, a consequence of renal disease, and hence irreversible by steroid administration.

Hyponatremia with excessive renal salt loss is seen in other conditions in which, apparently, the affected organ is far removed from the kidney and adrenal glands. It has been recognized that certain patients with pneumonia, congestive heart failure, peritonitis, tuberculous meningitis and particularly pulmonary tuberculosis may manifest evidence of salt depletion.[10,11] The urine contains abundant salt and administered salt is quickly excreted. A small degree of salt depletion probably could not be recognized since the clinical picture is dominated by a primary process that may itself resemble certain aspects of salt depletion. Winkler and Crankshaw[10] reported 14 cases of pulmonary tuberculosis in which large amounts of sodium chloride were excreted in the urine in the presence of lowered blood levels. The addition of 10 to 15 gm. of salt to the diet proved incapable of maintaining normal blood levels. Autopsies on 2 patients revealed anatomically normal adrenal glands and kidneys.[10] Rapoport and his associates studied 3 children with tuberculous meningitis who showed excessive renal salt loss. The nonprotein nitrogen and glomerular filtration rates were normal. Concentration tests indicated grossly normal distal tubular function. Post-mortem examination on 2 of these patients gave no evidence of adrenal or renal disease that could explain the salt loss.[11]

Other states exhibiting hyponatremia, chloruresis and dehydration, such as those produced by mercurial diuresis and those seen in the recovery phase of acute renal failure, will seldom cause diagnostic difficulty in differentiation from salt-losing nephritis.

The inability of the kidneys to conserve salt efficiently is usual in chronic renal disease although the loss of amounts sufficient to cause symptoms that dominate the clinical picture and simulate adrenocortical insufficiency is rare. It is not unusual, however, to observe that patients with chronic nephritis who have been placed on a low-salt diet to control edema formation may become somewhat dehydrated and then show a striking improvement when 1 to 5 gm. of salt is restored to the diet.[2] It is likely, nevertheless, that salt-losing nephritis is a particular variant of chronic Bright's disease that differs from the more usual forms in more respects than a simple quantitative increase in the amount of salt lost in the urine. Therefore, we propose certain minimum criteria that we believe should be met for the diagnosis of salt-losing nephritis as distinct from other salt-losing states: signs and symptoms consistent with dehydration are present on a normal salt intake (5-8 gm. per day) and can be relieved by an intake of 10 to 20 gm. of salt per day; the clinical state cannot be relieved by desoxycorticosterone acetate or, alternatively, steroids are present in the urine in normal amounts; and evidence of renal disease is present (low specific gravity, polyuria, elevated plasma urea and creatinine and anemia) and persists on high-salt intake.

We have divided the published cases of salt-losing nephritis into three groups according to how adequately they meet the foregoing criteria. The first group consists of 6 cases (those of Thorn and his associates,[2] Sawyer and Solez,[3] Nussbaum, Bernhard and Mattia,[4] Murphy et al.[8] and Murphy, Settimi and Kozokoff[9]*), which meet the proposed criteria and from which it is possible to draw a composite picture of the illness. The patients tend to be young (third and fourth decades). They give no history of renal disease except polyuria and nocturia. The onset of symptoms, which mimic adrenocortical insufficiency, — weakness, nausea, vomiting, fatigue, weight loss and muscle cramps, — is insidious.[2-4,7,8] The blood pressure is normal or low; heart size and function are normal, and funduscopic examination is negative. The urine shows a low, fixed specific gravity (usually below 1.010), with little or no protein, and with few formed elements in the sediment.[2-4,8,9] The usual disturbances in blood chemistry, common to all patients with advanced renal disease, are present, with the important addition of low plasma sodium and chloride and evidence of a large urinary content of these electrolytes. Steroids are present in normal amounts in the twenty-four-hour urinary volume. Desoxycorticosterone acetate is ineffective in decreasing salt excretion.[2-4,8,9] The addition of large amounts of sodium chloride (with or without sodium bicarbonate) to the diet causes the acute symptoms to subside rapidly and reduces the symptomatology to that attributable to uremia per se. Patients can tolerate 15 to 20 gm. of sodium chloride daily with no blood-pressure elevation or edema formation, even in the presence of the high degree of renal impairment.

A second group consists of 3 cases that possibly meet the proposed criteria (those of Borst,[5] Cheyne and Whitehead,[7] and Murphy et al.[8]†). These cases, in contrast to the first group, fulfill some but not all of the essential criteria. One case was associated with miliary tuberculosis,[5] and in another there was a definite past history of kidney disease and the patient had marked proteinuria.[9]† The third case required only minimal supplementary amounts of salt during therapy.[7]

A third group consists of 5 cases (those of Joiner and Thorne[6] and Murphy and his co-workers[9]‡

*Includes the case of a thirty-five-year-old man only.
†Includes the case of a fifty-three-year-old man only.
‡Includes cases of male patients twenty-five and twenty-seven years old.

that meet the proposed criteria. Some of these cases probably represent hyponatremia of chronic disease. Others were not under observation long enough for proper and complete diagnostic procedures to be carried out. The case presented above closely resembles several of the reported cases in which the patients were treated as having Addison's disease until other evidence indicated the real entity.[2-4] Although serious consideration of primary adrenal disease was obviated by early response to nonspecific therapy, absence of pigmentation and the presence of marked renal insufficiency, it was at first believed that the patient might be recovering from acute toxic nephritis. However, the absence of an oliguric phase or, indeed, any severe illness before admission, together with failure to discover a nephrotoxic agent, ruled out acute renal disease. The blood urea nitrogen, nonprotein nitrogen and blood creatinine in cases of salt-losing nephritis improve as the salt depletion is corrected but remain elevated, indicating the degree of renal damage present. Acidosis of a slight to moderate degree is usually present.[2,8] Frequently, the plasma sodium remains below 135 milliequiv. per liter in spite of large oral salt intake.[8] An elevated plasma potassium is noted occasionally (as in the case reported above and in others[4,8]), and may be a nonspecific consequence of the acidosis. The total protein is frequently elevated initially, indicating hemoconcentration, but nothing in this finding or in the altered blood calcium and phosphorus is characteristic of this disease. A mild to moderate anemia, usually normochromic and normocytic, is present.[2-4,8,9] The urinary output is abundant and varies from 1.5 to 3 or even more liters daily.

In cases examined at post-mortem examination the pathology has varied. In some, the pathological findings have been consistent with glomerulonephritis, as in the case reported above.[2,3,9] Others have attributed the primary disease to pyelonephritis.[4,6,8] Bilateral cystic disease has been reported.[5] Enticknap[12] examined microscopically 8 of the reported cases of salt-losing nephritis and believed that pyelonephritis was certainly present in 4 and probably present in 6. Three cases[5,6] were associated with tuberculosis, and it is difficult to know whether the renal salt loss was due to anatomically diseased kidneys or to the presence of tuberculosis itself.

It is our opinion, shared by others,[2,4] that salt-losing nephritis is probably a variant of chronic glomerulonephritis or pyelonephritis in which deterioration of tubular function for the reabsorption of sodium chloride has proceeded more rapidly than deterioration of glomerular function. The prostration of the patients and its relief by salt are so dramatic, however, that the term warrants retention for the designation of a separate clinical entity. Simple replacement therapy with sodium chloride and sodium bicarbonate may lead to partial or almost complete rehabilitation and allow months to years of comfortable and productive life.

Summary

An additional case of salt-losing nephritis simulating adrenocortical insufficiency is described.

Diagnostic criteria are proposed, based on published cases, to distinguish salt-losing nephritis from other salt-losing conditions.

The salient clinical, laboratory and pathological findings in cases reported in the literature are reviewed according to the proposed criteria.

References

1. Peters, J. P., Wakeman, A. M., Eisenman, A. J., and Lee, C. Total acid-base equilibrium of plasma in health and disease. X. Acidosis of nephritis. *J. Clin. Investigation* **6**:517-549, 1929.
2. Thorn, G. W., Koepf, G. F., and Clinton, M., Jr. Renal failure simulating adrenocortical insufficiency. *New Eng. J. Med.* **231**: 76-85, 1944.
3. Sawyer, W. H., and Solez, C. Salt-losing nephritis simulating adrenocortical insufficiency: report of case. *New Eng. J. Med.* **240**:210-215, 1949.
4. Nussbaum, H. E., Bernhard, W. G., and Mattia, V. D., Jr. Chronic pyelonephritis simulating adenocortical insufficiency. *New Eng. J. Med.* **246**:289-293, 1952.
5. Borst, J. R. Disturbances in water- and salt metabolism in final stage of chronic renal insufficiency. *Acta med. Scandinav.* **136**: 1-8, 1949.
6. Joiner, C. L., and Thorne, M. G. Salt-losing nephritis. *Lancet* **2**:454-458, 1952.
7. Cheyne, A. L., and Whitehead, T. P. Thorn's syndrome following excessive ingestion of alkalis. *Lancet* **1**:550-552, 1954.
8. Murphy, R. V., Coffman, E. W., Pringle, B. H., and Iseri, L. T. Studies of sodium and potassium metabolism in salt-losing nephritis. *Arch. Int. Med.* **90**:750-762, 1952.
9. Murphy, F. D., Settimi, A. L., and Kozokoff, N. J. Renal disease with salt losing syndrome: report of four cases of so-called "salt losing nephritis." *Ann. Int. Med.* **38**:1160-1176, 1953.
10. Winkler, A. W., and Crankshaw, O. F. Chloride depletion in conditions other than Addison's disease. *J. Clin. Investigation* **17**: 1-6, 1938.
11. Rapoport, S., West, C. D., and Brodsky, W. A. Salt losing conditions: renal defect in tuberculous meningitis. *J. Lab. & Clin. Med.* **37**:550-561, 1951.
12. Enticknap, J. B. Condition of kidneys in salt-losing nephritis. *Lancet* **2**:458-461, 1952.

ANORECTAL DISEASE IN THE COMMUNITY

With Special Reference to Detection of Rectal Cancer

GEORGE S. SPEARE, M.D.*

BOSTON

THE material in this paper is derived from an analysis of 400 cases seen in the Rectal Clinic of the Brusch Medical Center in Cambridge during the last two years. The purpose of the study is twofold: to show the incidence and discuss the diagnosis and treatment of the more common anorectal diseases in the community; and to consider early detection of rectal cancer and precancerous conditions, such as polyps.

The patients fall into two groups: 250 with symptoms of anorectal disease; and 150 who reported for general health examination and were given proctoscopic examinations for the detection of rectal cancer and other precancerous lesions. Fifty-seven per cent of these patients were male, and 43 per cent were female. The ages varied from two and a half to eighty years.

During the period covered by this study, there were 10,000 general admissions to the Clinic, all general-practice patients, except for obstetrics. Of these, 5050 were male, and 4950 were female patients. Although the number of patients in this series is small, the findings are considered significant because the patients went to the doctor for the first time for their present illness or for a general health examination. They were not screened previously by other doctors and referred to the Clinic for specialty examinations as most of the patients seen in the large metropolitan teaching hospitals are. Thus, the rectal disease found in these patients is believed to reflect the prevalence in the general population of the community.

All patients were examined by one man (myself), assuring uniformity of observations. The following technic was used throughout: a detailed history of proctologic disease was taken; an abdominal palpation was done in the supine position; the patient was then placed in the left lateral position, and the perianal region was inspected; a digital examination was performed; and the anus and anorectal region were inspected by means of a short, fenestrated anoscope with direct illumination. The patient was then placed in the knee-shoulder position, and proctosigmoidoscopy with an instrument 23 cm. long was carried out. The patients were prepared with a soapsuds enema, taken at home about two or three hours before they reported to the clinic. In a few cases, when the rectum still contained fecal material, the Fleet disposable enema was found to be helpful. It was possible to pass the instrument above the rectosigmoid in 57 per cent of the patients and only to the rectosigmoid in 43 per cent. No strenuous effort was made to introduce the instrument above the rectosigmoid if the sigmoid angle was sharp or if the patient experienced undue discomfort.

*Clinical associate in surgery, Massachusetts General Hospital.

ANALYSIS OF 150 EXAMINATIONS

One hundred and fifty patients were examined as a part of a cancer-detection program. None of these people had any symptoms of anorectal or colonic disease. Their ages varied from forty to eighty years. There were 95 men and 55 women. Table 1 shows the pathologic conditions disclosed by the examination.

One of the significant findings in the analysis of these cases was the discovery of 2 cancers (1.25 per cent). A cancer of the cecum was found on routine palpation of the abdomen in a sixty-three-year-old woman. The other was a cancer of the rectosigmoid, revealed by proctoscopic examination of a seventy-two-year-old man.

Of even greater significance was the discovery of 9 polyps, or 6 per cent, on routine proctoscopic examination. There were probably more polyps in the colons of these patients; only a few could be given barium-enema examinations.

The polyps were located in an area of the rectum and lower sigmoid, 10 to 20 cm. up from the anal sphincter. The sizes varied from 0.4 cm. to 1.5 cm. All were removed in the Clinic without hospitalization.

This is a small series of cases, and the findings cannot be conclusive. However, the 1.25 per cent prevalence of rectal and colonic neoplasms and the 6 per cent prevalence of rectal polyps in asymptomatic patients agree with those of larger series of cases reported in the literature,[1,2] and show that even in a small number of routine proctoscopies, one can be rewarded with the discovery of early cancer and premalignant lesions, such as polyps. It is generally accepted that polyps of the rectum and colon eventually degenerate into cancer[3-5] and that early diagnosis and treatment will save many lives.

There were hemorrhoids in 62 of 150 given health examinations at the Clinic (Table 1) — a prevalence of about 40 per cent in clinic patients over forty years of age. However, half these hemorrhoids were very small and of no clinical significance, leaving only 30 cases (20 per cent) that could be clinically considered hemorrhoids. Of these, 23 were internal hemorrhoids of moderate size that usually cause no

symptoms except some bleeding occasionally when traumatized by the passage of hard stool. Only 7 hemorrhoids were large, both external and internal, and required surgical treatment. Many of these patients on questioning admitted symptoms but did not consider them important enough to require medical advice.

TABLE 1. *Pathologic Conditions Found in 150 Routine Proctoscopies.*

CONDITION	No. OF CASES
Hemorrhoids	62
Rectal polyps	9
Carcinoma	2
Pruritus ani	8
Fissures	3
Enlarged anal papillae	5
Multiple miliary sebaceous cysts	3
Low proctitis	4
Tight anus	5
Nervous colon	2
Negative examination	49

ANALYSIS OF 350 CASES OF ANORECTAL DISEASE

This group of cases consisted of 250 patients who had symptoms of anorectal colonic disease and 100 of the health-survey patients in whom some anorectal lesion was found on routine examination. Table 2 shows the various pathologic conditions found in these patients, many of whom had more than one anorectal disease.

RELATION OF CANCER TO THIS SERIES

Ten cases in this series were diagnosed as cancer. The ages of the patients varied from forty-three to seventy-two years; 5 were men, and 5 were women. Four lesions were found in the rectum, 2 in the rectosigmoid, 1 in the descending colon, 1 in the splenic flexure, 1 in the right transverse colon, and 1 in the cecum. Four of the lesions (40 per cent) were within the reach of the examining finger, and 6 (60 per cent) were within the reach of the sigmoidoscope. All 10 were resected. Abdominoperineal resection was done in 5 patients. In 1 case, that of a seventy-two-year-old man with cardiac decompensation and a rectosigmoid lesion, a Hartman procedure was carried out, leaving the rectal pouch in place. Of the 4 cancers of the colon, 2 were removed by left-sided colectomy, without proximal decompression, and the other 2 by one-stage right-sided colectomy. One man died on the eighteenth postoperative day. This patient had a large, Grade 3 carcinoma of the rectum, with obstruction, perforation and abscess. Intestinal obstruction developed on the eighth postoperative day by adhesion of the terminal ileum to the pelvic suture line of the peritoneal floor. This was surgically corrected, but the patient kept on doing poorly, and was incoherent and confused. A small-bowel fistula occurred through the perineal wound, and he died of massive intestinal hemorrhage eighteen days after the first operation. Autopsy was not permitted. Two other patients died of metastases one and two years after the operation. The other 7 patients are alive and apparently free of disease, a few months to two years after operation.

MISCELLANEOUS CASES

There were several interesting miscellaneous cases in this series. In 1 (that of a sixty-three-year-old woman with moderate anal stenosis) a walnut-sized fecalith was mistaken for a polyp of the sigmoid on two barium-enema examinations; fortunately, the fecalith was eventually visualized through the sigmoidoscope and removed by rectum. Two patients showed marked melanosis coli. Both had been taking cascara sagrada for a long time. It is now established that melanosis coli is caused by the ingestion of one of the anthracene compounds,[6,7] most commonly, cascara. In 1 case masses of condyloma acuminatum were promptly cleared by the application of 25 per cent podophyllin ointment. In 1 case of a twice-recurrent fistula in ano, a stone (fecalith) was found

TABLE 2. *Pathologic Conditions in 350 Patients.**

CONDITION	No. OF CASES
Hemorrhoids	199
Pruritus ani	55
Polyps	25
Fissures	31
Cancer	10
Fibrous polyps	8
Large papillae	13
Thrombosis of external hemorrhoids	12
Anal stenosis	10
Low proctitis	15
Fistula in ano	4
Ischiorectal abscess	3
Multiple miliary sebaceous cysts	5
Redundant rectal mucosa	11
Ulcerative colitis	4
Acute cryptitis	2
Anal incontinence	2
Coccygodynia	2
Nervous colon	7
Melanosis coli	2
Proctalgia fugax	2
Fecaliths	2
Dyschezia (due to rectocele)	2
Condyloma acuminatum	1

*250 with rectal symptoms, & 100 with disease found on routine health examination.

at the bottom of the fistulous tract. In the 2 cases of proctalgia fugax, or nervous spasm of the rectum, 1 man who had had attacks for ten years was able to abort the attacks by instilling 60 ml. of warm water in his rectum. He always carried a rubber syringe in his pocket, and whenever rectal spasm began, he went to his room at once and gave himself the hot-water enema, with immediate and complete relief.

Eight patients had fibrous polyps of the anus, and 12 had enlarged papillae. Both these lesions represent the same disease. When the enlarged papilla reaches the size of 1 to 3 cm. in diameter, it looks like a pedunculated polyp attached to the mucocutaneous line. These polyps cause symptoms by obstructing the anal orifice. They can readily be removed under local anesthesia in the clinic. They do not become malignant. The enlarged papillae usually cause no symptoms and need no treatment. Chronic infection in the crypts, with fibrosis and lymphatic obstruction, is probably the cause of the enlargement of the anal papillae.

Summary and Conclusions

Of 150 patients over forty years of age who had a routine anorectal and sigmoidoscopic examination, 1.25 per cent were found to have carcinoma, 6 per cent polyps of the rectum, 20 per cent hemorrhoids, 5 per cent pruritus ani, 2 per cent fissures in ano, and 3.5 per cent enlarged papillae and fibrous polyps. Thirty-three per cent showed no anorectal disease.

In 10,000 consecutive admissions of general-practice patients, excluding obstetrics, 350, or 3.5 per cent, showed the presence of one or more anorectal or colonic diseases. Of these, 110, or 30 per cent, had hemorrhoids, 55, or 15 per cent, had pruritus ani, 31, or 10 per cent, had fissures in ano, 25, or 7 per cent, had polyps, 10, or 3.5 per cent, had cancer, 20, or 7 per cent, had enlarged papillae or fibrous polyps, 15, or 5.3 per cent, had low proctitis, 10, or 3.5 per cent, had some degree of anal stenosis, 11, or 3.5 per cent, had redundant prolapsing rectal mucosa, and 7, or 3 per cent, had fistula in ano and abscess.

Digital and proctosigmoidoscopic examination, routinely done on all patients, is a simple and effective method of detection of rectal cancer.

353 Commonwealth Avenue

References

1. Runyeon, F. G. Sigmoidoscopy: its clinical importance to practitioner: chairman's address. *J.A.M.A.* **147**:913, 1951.
2. Smith, E. T., Stephenson, W. H., and Anderson, R. M. Value of routine proctosigmoidoscopy. *West. J. Surg.* **63**:628-630, 1955.
3. Colcock, B. P. Carcinoma of right colon. *New Eng. J. Med.* **246**: 391-396, 1952.
4. Swinton, N. W., and Doane, W. A. Significance of polyps of colon and rectum. *New Eng. J. Med.* **249**:673-677, 1953.
5. Welch, C. E., McKittrick, J. B., and Behringer, G. Polyps of rectum and colon and their relation to cancer. *New Eng. J. Med.* **247**:959-965, 1952.
6. Speare, G. S. Melanosis coli: experimental observations on its production and elimination in twenty-three cases. *Am. J. Surg.* **82**: 631-637, 1951.
7. Bockus, H. L., Willard, J. H., and Bank, J. Melanosis coli: etiologic significance of anthracene laxatives: report of 41 cases. *J. A. M. A.* **101**:1-6, 1933.

MEDICAL PROGRESS

MANAGEMENT OF PYELONEPHRITIS (Concluded)*

Harry A. Derow, M.D.†

BOSTON

Diagnosis

Longcope and Winkenwerder[86] emphasized the diagnostic challenge that pyelonephritis presents as follows:

> From the significant data that are now available, it should be possible to recognize this form of renal disease long before the critical stage has been reached in the destruction of renal tissue.

Of fundamental importance in the diagnosis of pyelonephritis is the need for the physician to appreciate that the symptomatology, if present, may or may not suggest urinary-tract involvement and that careful urinalysis and bacteriologic study of the urine often reveal abnormalities that may be consistent with the disease.

It must be emphasized that the patients with pyelonephritis whom the physician is usually called upon to treat are those who present *overt* phenomena — such urinary-tract symptoms as flank or costovertebralangle pain, urgency, frequency and dysuria, with or without chills, fever, headache, prostration, gastrointestinal disturbances, abdominal distention and ileus. The diagnosis in such cases is not difficult because unmistakable urinary abnormalities are usually found.

*From the Medical Service and Nephritic Clinic, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.

†Assistant clinical professor of medicine, Harvard Medical School; visiting physician and head of Nephritic Clinic, Beth Israel Hospital.

When the symptoms suggest abdominal surgical disease, or if nonspecific phenomena such as fever, feeling below par and recurrent myalgias predominate, the urinary findings may be consistent with pyelonephritis. The diagnosis in such cases may be difficult.

The asymptomatic patient with urinary abnormalities and the symptomatic patient with normal urine present the greatest problems in diagnosis. It should be pointed out that hypertension, benign or malignant, may supervene during the course of asymptomatic and rarely of symptomatic pyelonephritis, and may present a clinical picture that may mask the underlying inflammatory renal disease. Furthermore, the symptoms and signs of urinary-tract obstruction may completely overshadow those of renal involvement itself. Rarely, uremic symptoms bring the patient to the physician for the first time.

The differentiation of an initial attack of pyelonephritis and an exacerbation of a smoldering asymptomatic renal infection may be impossible unless the antecedent history and urinary findings are known.

The Urine

The importance of a properly obtained specimen of urine in all cases of suspected pyelonephritis cannot be overemphasized. A "clean" voided urine in the male or a specimen obtained by catheterization in the female should be examined immediately and studied bacteriologically.

The urinary findings in pyelonephritis may vary considerably from time to time.[40,41] It should be emphasized that the urine may be normal when the acute or chronic inflammatory process and the subsequent scarring are localized in the interstitial tissue without communicating with the tubular system.

In acute pyelonephritis, proteinuria of varying degree is usually present. Microscopical examination of the urine often reveals pyuria, bacteriuria and occasionally hematuria and cylindruria.

In subacute or chronic pyelonephritis, proteinuria may be moderate, minimal or at times even absent. Although pyuria and bacteriuria may be found together, either may be present without the other. Bacteriuria may be absent for long periods despite the continued presence of pus cells in the urine.

On the basis of studies with a gentian-violet-safranine stain of the urinary sediment in pyelonephritis, Sternheimer and Malbin[42] described large leukocytes with specifically staining nuclei and cytoplasm and cytoplasmic granules showing brownian movement (glitter cells). These findings are not always present in typical cases.

Bacteriologic Examination of the Urine

The rational management of the disease depends to a large extent upon appropriate bacteriologic studies of the urine, and the application of sound clinical judgment in interpreting and evaluating the findings.

The Gram-stained smear of the freshly collected urine, or of the centrifuged sediment, will reveal organisms present in significant numbers, their morphology (that is, whether they are bacilli or cocci) and their staining reactions. Identification of the actual organisms present may be determined from cultures of the fresh urine on appropriate media.

The advantages of quantitative bacterial counts on urine specimens using the agar pour-plate technic was emphasized by Marple[5] in 1940, and more recently re-emphasized by Kass[6,8] and Sanford et al.[7] Kass's careful and extensive studies revealed that *significant* bacteriuria is probably present when the bacterial counts are 10^5 or more per milliliter of urine and that counts significantly lower than this probably represent contamination. However, the limitations of this quantitative approach to the diagnosis of significant bacteriuria should be stressed. In the presence of active pyelonephritis, bacterial counts below 10^5 per milliliter of urine may be found when a bacteriostatic agent is in the urine; when the rate of urine flow is rapid, the number of bacteria discharged from the kidney is small, and pooling of urine in the bladder for a long enough time to permit multiplication to significant levels has not occurred; when urinary pH and dilution have limited the degree of bacterial multiplication in urine; when fastidious organisms that grow poorly in urine are encountered; when, in obstruction of the ureter, bladder urine is free of bacteria; and when the infection is in limited areas of the kidney not directly communicating with renal tubules.[6,8]

It should be obvious that in any quantitative evaluation of urinary bacteria the care exercised in obtaining the specimens of urine and the speed with which they are processed are of the utmost importance. The specimens of urine should either be examined within an hour after collection or immediately refrigerated for subsequent study within forty-eight hours. For practical clinical purposes the Gram stain of the freshly collected and unsedimented urine will differentiate contamination from infection, since organisms are readily found in stained specimens of urine when about 10^5 bacteria or more per milliliter are present.

Antimicrobial sensitivity tests should be undertaken to determine which agent or combination of agents may be effective against the *significant* bacterial population found in the urine. The "disk" method may provide data not only about which antimicrobials are likely to inhibit the infecting bacteria but also which agents should not be used because the organisms appear resistant. However, the "tube-dilution" tests may yield information of a quantitative nature — for example, the antimicrobial concentration that is capable of bacteriostatic or

bacteriocidal effect. Consultation with the bacteriologist will frequently result in valuable guidance in management.

X-Ray Examination

A good plain film of the entire urinary tract will permit an estimate of the size of each kidney and the detection of radiopaque calculi. If the kidneys are capable of concentrating the dye, intravenous pyelography should be performed to establish the presence of two kidneys, the functional capacity of each, deviations in gross size and shape, deformities in the calyceal, pelvic and ureteral architecture and obstructive phenomena. In acute pyelonephritis, the pyelogram may show no deviation from normal in spite of widespread inflammatory changes in the kidneys. The outline of the pyelogram in chronic pyelonephritis may or may not be altered. The changes consist of various deformities of the calyxes, pelves and ureters.

Role of the Urologist

Urologic investigation may be indicated in cases with gross hematuria, severe pain, recurrent acute attacks, persistent lower-urinary-tract symptoms, constant bacteriuria or pyuria, or both, and unsatisfactory intravenous pyelograms. Such investigation should establish the presence or absence of complicating lesions such as obstruction, calculi and tumor, as well as provide urine from each kidney for routine examination and bacteriologic study and data pertaining to function of each kidney and visualization of the ureters, pelves and calyxes. The diagnosis of unilateral pyelonephritis can be made only by this method.

Needle Biopsy of the Kidney

Since acute and chronic pyelonephritis may give rise to focal areas of inflammation, needle biopsy of the kidney may miss such areas and yield normal renal tissue. However, in diffuse pyelonephritis with impairment of renal function, the biopsy specimen usually shows characteristic morphologic alterations.[43-45]

Culture of the renal-biopsy tissue may reveal organisms also present in the urine.[43] On the other hand Muehrcke et al.[44] recently reported positive bacteriologic cultures obtained from renal tissue in 5 patients whose cultures of the urine revealed no growth. These patients showed proteinuria, hematuria and impaired renal function. After the administration of appropriate antibiotics, the proteinuria and hematuria disappeared, and the kidney function was restored to normal. This clinical entity has been designated "bacterial nephritis." The pathological picture, based upon serial biopsies of the kidney, revealed marked periglomerular interstitial inflammation and focal necrotizing glomerulitis followed by hyalinization of some glomeruli, focal glomerular cellularity and foci of chronic inflammatory cells around hyalinized glomeruli.

Other Considerations

It should be emphasized that negative urinary cultures and normal-appearing pyelograms do not eliminate pyelonephritis as a possible cause of renal disease.

Primary hyperparathyroidism should always be considered a possible cause of renal calculi complicated by pyelonephritis.[46]

Prognosis

The prognosis of pyelonephritis depends on a number of considerations, which may be stated briefly as follows:

The stage of the disease when the patient is first seen.

The extent of the renal damage — focal or diffuse, unilateral or bilateral.

The status of renal function.

The presence of complicating or accessory conditions such as obstruction, calculi and neuromuscular disorders.

The degree of chronicity of the infection.

Sensitivity of the pathogenic bacteria in the urine to antimicrobial therapy.

Coexistence with diabetes mellitus.

Possibility of resolution of the renal lesion as a result of spontaneous healing or of therapy.

Frequency of recurrences.

Supervention of renal insufficiency or hypertension (or both) and its sequelae.

Recovery

Recovery from pyelonephritis may be difficult to ascertain definitely. Even though disappearance of urinary abnormalities and bacteriuria may occur, the possibility of residual infection in the interstitial tissue of the kidney is always present. However, spontaneous healing of acute uncomplicated pyelonephritis occurs frequently even in the absence of antimicrobial therapy. Furthermore, in the chronic form of uncomplicated pyelonephritis at least 20 per cent of patients eventually recover spontaneously.[47] Removal of obstruction or calculi may be followed by clearing of the renal disease. However, pyuria, bacteriuria and proteinuria may persist after the elimination of the complicating lesion.

Recurrences

After a period ranging from months to years pyelonephritis may recur in patients who appear to have recovered from the disease. In such cases it may be impossible to say whether there has been incomplete healing of the initial attack or complete healing with recurrence.

Chronicity

The patients who do not recover may continue to show pyuria or bacteriuria, or both, and proteinuria in varying amounts, with or without recurrent symptomatic episodes. In the presence of bilateral disease the progress of impairment of renal function may be very slow. Fulminating exacerbations of the disease or renal medullary necrosis may occur, causing death in acute uremia. Hypertension, occasionally of the malignant variety, may supervene before or after renal insufficiency appears. Death is usually due to uremia and less often to the consequences of hypertension or unrelated diseases.

Of fundamental importance in prognosis is the fact that the outlook is generally poor in cases in which renal insufficiency or hypertension or both have appeared.

Treatment

Since pyelonephritis is a bacterial infection of the kidney, the goal of treatment must be the complete eradication of such an infection before significant renal scarring has occurred. This is indeed a therapeutic challenge! How successfully it can be met will be evident from the following discussion.

Prophylaxis

Since catheterizations, inlying catheters and instrumentation of the urethra, bladder and ureters must be employed in a variety of clinical conditions, prophylactic antimicrobial therapy is often used to prevent urinary-tract infection. Recent reports indicate that such therapy not only may not prevent such an infection but also may be responsible for a greater incidence.[48,49] Furthermore, in the presence of infection, prophylaxis may reduce pyuria temporarily and replace susceptible with resistant bacteria.[50]

Role of the Urologist

The urologist may play a significant part in the treatment of pyelonephritis if demonstrable urinary-tract abnormalities such as obstruction and calculi are present. If nephrectomy is contemplated, the urologist must be certain that the contralateral kidney is adequate to support life.

Recurrent nephrolithiasis in patients with pyelonephritis requires careful study of the etiologic factors involved, as well as adequate analysis of a urinary calculus by crystallography or other methods. A regimen should be instituted to prevent, if possible, recurrent stone formation.[51-54]

Antimicrobial Treatment

The effectiveness of currently employed antimicrobial treatment of pyelonephritis depends upon the stage of the infection, — acute, recurrent or chronic, — the presence of recognizable urinary-tract abnormalities and the sensitivity of the pathogenic bacteria in the urine to the therapeutic agent. Eradication of the infection may be difficult or even impossible to achieve in chronic pyelonephritis because the bacteria in the scarred chronic inflammatory lesions may not be accessible or susceptible to the therapeutic agent.

Of fundamental importance in the antimicrobial therapy of initial *acute symptomatic cases of pyelonephritis* is the physician's awareness that most cases show single bacterial species, usually *Esch. coli*, in the urine,[6,14] are usually self-limited and often heal spontaneously. It should be emphasized that a variety of therapeutic agents, including acidification of the urine, mandelic acid, methenamine mandelate, sulfonamides, nitrofurantoin and antibiotics, may be highly effective in the treatment of such cases. In my experience and that of others[55] the antibacterial agent of choice should be one of the sulfonamides in a dosage of 4 to 6 gm. as soon as the diagnosis is established, followed by 1 gm. four times a day for a period of two weeks. If sulfonamide therapy fails to eradicate the bacteria from the urine, a course of nitrofurantoin may be given in dosage of 100 mg. administered four times a day for two weeks; this drug should be given with meals and the bedtime dose with milk to eliminate or minimize the nausea that may accompany the use of the drug. If such therapy has not eliminated the infecting organism from the urine or the patient's symptoms are not relieved, urologic investigation should be carried out and the indicated treatment instituted. In addition, urine culture and sensitivity studies should be done to determine the appropriate antibacterial agent for further therapy.

Before cases of *recurrent symptomatic pyelonephritis* or *asymptomatic chronic pyelonephritis* with bacteriuria and pyuria are subjected to therapy with antibacterial agents urologic investigation and cultures and sensitivity studies of the organisms isolated from each kidney should be undertaken. The indicated urologic treatment should be carried out, and the appropriate antibacterial agent prescribed for a period of two weeks. In the presence of symptoms antimicrobial therapy may relieve dysuria and frequency of urination by eradicating the bacteria or by reducing the bacterial count without eradicating all the bacteria in the urine. In asymptomatic cases with antimicrobial-resistant bacteriuria I have discontinued antibacterial therapy after many attempts to eradicate the bacteria in the urine proved unsuccessful. In some of these patients, followed over long periods, bacteria-free urine spontaneously developed whereas others continued to show the same or other types of resistant bacteria. Some authors[56] have made a plea for a much longer course of treatment than is usually employed, but their results are difficult to evaluate.

A study of the literature reveals many reports describing the immediate good results after the treatment of pyelonephritis with modern antibacterial agents. However, the longer the follow-up period after treatment, the more frequent relapse or reinfection will be. Many authors[6,57,58] have stated that in view of the present availability of antimicrobials, the results of therapy of pyelonephritis are not as good as might be expected. Stenderup et al.[57] found, in a study of 181 patients, that relapse or reinfection occurred not only in patients with urinary-tract abnormalities or a past history of infection but also, though less frequently, in those with no demonstrable complicating factors. Furthermore, Rhoads et al.,[58] in a report on 325 patients, more than 75 per cent of whom had demonstrable urinary obstruction, found that whereas more than half showed sterile urine after therapy, only 8 per cent were permanently cured. The latter group either were without obstruction originally or had undergone correction of the obstruction.

The difficulty in eradicating chronic urinary-tract infections in patients with diabetes mellitus was reported recently from the Joslin Clinic.[19] In a group of 52 patients treated by intensive use of antibiotics only 5 patients were "cured," 29 were "improved," and 18 were "unimproved." The fact that the urinary tract of a diabetic patient cannot tolerate contamination was re-emphasized in this report.

Kass[6] recently summarized the status of antibacterial treatment in chronic and complicated pyelonephritis as follows:

> Eradication of drug-resistant bacteria is possible more than 90 per cent of the time.
>
> Reinfection with drug-resistant bacteria occurs so frequently after the urine has become sterile that the permanent control rate in these infections is probably no greater than about 10 per cent.
>
> When reinfection occurs it is most often due to bacterial strains different from those originally present, although it may be due to the same species.
>
> Nosocomial infections play a large part in the reinfection of urinary tracts, probably through the medium of the catheter and similar instruments.

It is obvious that the antibacterial treatment of chronic pyelonephritis leaves much to be desired. The increased frequency in such cases of enterococci and members of the genera proteus, aerobacter and pseudomonas, all of which are resistant in varying degrees to the available antimicrobial agents, undoubtedly contributes to the unsatisfactory and discouraging results.[6,14]

Pyelonephritis is similar to glomerulonephritis in the following respects: most of the patients with initially acute symptoms recover completely whereas most of the chronic cases develop insidiously and continue with or without exacerbations.

In view of the considerations mentioned above, the advertisements appearing in medical journals and the voluminous literature received daily by physicians describing the virtues of antibacterial agents manufactured by pharmaceutical companies deserve comment. In a personal survey of such printed material prepared by pharmaceutical companies, I was impressed with many uncritical statements and unjustified claims for the efficacy of the antibacterial agents in the therapy of pyelonephritis. Statements indicating that a certain agent "must now be considered the drug of choice in both acute and chronic urinary-tract infection" are misleading and based upon inadequate data. Indeed, such claims may be dangerous to the welfare of the patient because no mention is made of the problem of bacterial resistance or reinfection or the need to establish whether the infection is complicated. Furthermore, the need for follow-up studies to ensure the permanency of elimination of bacteria from the urine is not mentioned at all.

Pyelonephritis of Pregnancy

The management of pyelonephritis that arises during pregnancy or the post-partum period is similar to that employed in nongravid patients. Usually, the initial episode responds favorably to antibacterial therapy and a large urinary volume. However, if pyelonephritis antedated the pregnancy and is recurrent and symptomatic or asymptomatic, with bacteriuria, pyuria and proteinuria, the therapeutic results are similar to those described above in nonpregnant cases. Urologic investigation should be performed to establish the absence of complicating factors and to institute the indicated therapy if any are found.

Hypertension[20]

The treatment of hypertension in bilateral pyelonephritis without renal insufficiency may be undertaken to prevent or reduce the strain upon the heart. Drugs, diet therapy and even sympathectomy, either singly or in various combinations, have been successful in reducing the elevated blood pressure in many patients.

In chronic renal insufficiency, therapy directed at diminishing the hypertension is often hazardous because of the delayed excretion of drugs with severe toxic potentialities and the worsening of existing electrolyte derangements. However, it may be possible to reduce the azotemia and slow the progress of the renal disease by moderate lowering of the severe hypertension in chronic renal insufficiency. Although sympathectomy has afforded symptomatic relief in some of these patients, this procedure is usually contraindicated.

Hypertension Due to Unilateral Pyelonephritis

It should be pointed out that hypertension may be absent in the presence of severe atrophic unilateral

pyelonephritis. However, well documented cases in which hypertension was cured by the removal of the diseased kidney in patients with unilateral pyelonephritis have been collected and critically reviewed by several authors.[54,59,60] Nephrectomy may be undertaken for the relief of hypertension if the affected kidney is nonfunctioning and the contralateral kidney is free from disease and shows normal function.

Homotransplantation of a Single Kidney

The management of severe renal insufficiency that may appear after a varying period during the course of nonobstructive bilateral pyelonephritis or similar involvement of the remaining kidney after the contralateral organ has been removed for surgical reasons is usually unsatisfactory. A more hopeful approach is available if the patient is an identical twin and the healthy twin possesses two normally functioning kidneys free from disease. Successful homotransplantation of the human kidney between identical twins, with survival of the homograft for twelve months up to the time of the report, has been described by Merrill et al.[61]

Emotional Aspects

Much has been written concerning the emotional aspects of chronic illness and their manifestations in the patient and his family as well as in the physician responsible for the patient's care. Pyelonephritis is often a chronic illness, but there are special problems that pertain to this disorder that are unique and often cause anxiety in the patient and his family and worry in the physician.

To the patient and his family, the *individual episode of urinary-tract symptoms is the illness* that imposes certain restrictions and often requires repeated hospitalization for investigative procedures and treatment. If the patient becomes free of symptoms, it may be difficult to obtain his co-operation for the necessary studies to establish whether recovery or continued bacterial infection of the urine has occurred. On the other hand, if he does co-operate and is advised to take a course of appropriate antibacterial medication to eradicate the bacteria in the urine, he may complain of the cost of the medication or the toxic manifestations caused by the agent especially if he felt well before the institution of the therapy. The need to obtain catheterized samples of urine in the female may present a variety of emotional problems. Recurrent symptomatic attacks are discouraging to the patient because he must be subjected to a repetition of what he has gone through previously. The need to undergo the removal of calculi, surgical relief of obstruction or nephrectomy requires additional hospitalization and increases the anxiety the patient already has. The need for continuous follow-up study may be rejected by the patient because he may resent taking medication or being subjected to further procedures and hospitalization when he is free of symptoms.

As for the physician, unless he is familiar with the vagaries of pyelonephritis, he may be subjected to worry as a result of his own ignorance and also by the need to relieve the anxieties of the patient or his family imposed by the disorder and its therapy. It is therefore essential that the physician feel secure in his knowledge of pyelonephritis. He should be prepared to tell the patient or his family what is and what is not known about the disorder — that is, its cause, duration, recovery, recurrences, final outcome and so on — to avoid such anxiety as uncertainty may produce. Successful management of emotional reactions in pyelonephritis is indeed complex, taxing the resourcefulness and understanding of the physician.

References

40. Derow, H. A. Diagnostic value of serial measurements of albuminuria in ambulatory patients. *New Eng. J. Med.* **227**:827-829, 1942.
41. King, S. E. Conditioned urinary protein excretion test in study of chronic and obscure proteinuria. *Arch. Int. Med.* **97**:511-520, 1956.
42. Sternheimer, R., and Malbin, B. Clinical recognition of pyelonephritis, with new stain for urinary sediments. *Am. J. Med.* **11**: 312-323, 1951.
43. Kipnis, G. P., Jackson, G. G., Dallenbach, F. D., and Schoenberger, J. A. Renal biopsy in pyelonephritis. *Arch. Int. Med.* **95**: 445-459, 1955.
44. Muehrcke, R. C., Kark, R. M., and Pirani, C. L. Biopsy of kidney in diagnosis and management of renal disease. *New Eng. J. Med.* **253**:537-546, 1955.
45. Kark, R. M., Muehrcke, R. C., Pirani, C. L., and Pollak, V. E. Clinical value of renal biopsy. *Ann. Int. Med.* **43**:807-847, 1955.
46. Albright, F., Baird, P. C., Cope, O., and Bloomberg, E. Studies on physiology of parathyroid glands. IV. Renal complications of hyperparathyroidism. *Am. J. M. Sc.* **187**:49-65, 1934.
47. Braasch, W. F. Clinical data concerning chronic pyelonephritis. *J. Urol.* **39**:1-33, 1938.
48. Garrod, L. P., Shooter, R. A., and Curwen, M. P. Results of chemotherapy in urinary infections. *Brit. M. J.* **2**:1003-1008, 1954.
49. Durham, M. P., Shooter, R. A., and Curwen, M. P. Failure of sulphonamides to prevent urinary infections after vaginal surgery. *Brit. M. J.* **2**:1008, 1954.
50. Blakey, P. R. Experiences with terramycin in urinary and genital tract infections. *Canad. M. A. J.* **66**:151-154, 1952.
51. Higgins, C. C. Nephrolithiasis. *M. Clin. North America* **39**: 1073-1079, 1955.
52. Prien, E. L., and Walker, B. S. Salicylate therapy of recurrent calcium urolithiasis. *New Eng. J. Med.* **253**:446-451, 1955.
53. Baker, R., and Connelly, J. P. Bilateral and recurrent renal calculi: evidence indicating renal collagen abnormality and results of salicylate therapy. *J.A.M.A.* **160**:1106-1110, 1956.
54. Marshall, V. F., Oppenheimer, G. D., Slaughter, G. W., Spellman, R. M., and Twinem, F. P. Renal calculi (transcription of panel meeting). *Bull. New York Acad. Med.* **32**:293-317, 1956.
55. Cook, E. N. Management of infections of urinary tract. *Ann. Int. Med.* **43**:316-322, 1955.
56. Stansfeld, J. M., and Webb, J. K. Plea for longer treatment of chronic pyelonephritis in children. *Brit. M. J.* **1**:616-618, 1954.
57. Stenderup, A., Kissmeyer-Nielsen, F., and Linnet-Jepsen, P. Chemotherapy in infections of urinary tract. *Acta med. Scandinav.* **144**:124-136, 1952.
58. Rhoads, P. S., Billings, C. E., and O'Conor, V. J. Antibacterial management of urinary tract infections. *J.A.M.A.* **148**:165-170, 1952.
59. Smith, H. W. *The Kidney: Structure and function in health and disease.* 1049 pp. New York: Oxford, 1951.
60. Pickering, G. W. *High Blood Pressure.* 547 pp. New York: Grune and Stratton, 1955.
61. Merrill, J. P., Murray, J. E., Harrison, J. H., and Guild, W. R. Successful homotransplantation of human kidney between identical twins. *J.A.M.A.* **160**:277-282, 1956.

MEDICAL INTELLIGENCE

POLIOMYELITIS VACCINATION IN SOUTHEAST MASSACHUSETTS IN 1955*

Influence of a Single Dose of Salk Vaccine

FRANK RANDOLF PHILBROOK, M.D.,† AND THEODORE H. INGALLS, M.D.‡

BOSTON

AFTER confirmation of the efficacy of the Salk vaccine by the 1954 field trial, the outbreak of poliomyelitis during April, 1955, in Idaho[1] acted as a damper on immediate endorsement by practicing physicians and public-health authorities of state-wide programs of immunization; and also upon ready acceptance of the proffered product on the part of parents. The first consideration became one of safety. Specifically, necessity was demonstrated for controlling precisely the circumstances of manufacture, and especially the details of filtration and neutralization with formaldehyde. The result was a safer vaccine, but would it be as effective as its predecessor — or less effective? No one knew in May, 1955.

TABLE 1. *Poliomyelitis Rates in 5 Contiguous Southeastern Massachusetts Communities, 1955.*

COMMUNITY	TOTAL 1955 POPULATION	TOTAL 1955 CASES	RATE
			per 100,000
Weymouth	42,747	96	225
Randolph	13,539	32	236
Holbrook	6,686	13	194
Braintree	28,005	46	164
Quincy	84,200	131	156
Totals	175,177	318	182

Because of the sequence of events and because of various theoretical and logistic problems that have been reviewed elsewhere[2] Massachusetts health officials adopted a conservative attitude toward the use of the vaccine in the summer of 1955, and made plans for a critical evaluation of its effectiveness and possible dangers. The over-all experience for the summer of 1955 was subsequently analyzed and recounted in the *Journal*.[3] This study approaches the problem independently by evaluating only a selected portion of the state-wide experiences — that of 5 contiguous townships representing a sample of the heavily hit region south of Boston (Table 1). Attention is centered on the ability of one dose of the improved vaccine to protect children six, seven and eight years of age in July, August and September, 1955.

From a purely scientific point of view the children participating in this trial probably should have been paired and given vaccines at random — approximately half given the perfected Salk vaccine and approximately half given a gelatin control as in the 1954 field trial. However, for evident reasons, that plan was not even considered at the time; nor is it likely that poliomyelitis vaccines of the future will again be tested against controls — in the United States at least. The uninoculated fraction of the population will get smaller and smaller, and improved products will presumably be evaluated against their predecessors. In 1955, therefore, as a practical expedient, advantage was taken of the fact that about as many parents and physicians had adopted a wait-and-see attitude as had signed up for injection of the new vaccine. This had just become available

TABLE 2. *Age-Specific Rates and Vaccination for Poliomyelitis in 5 Contiguous Massachusetts Towns, 1955.*

TOWN	NO. OF CHILDREN 6 THROUGH 8 YR. OF AGE	NO. OF CHILDREN VACCINATED*	NO. OF CASES OF POLIOMYELITIS			RATE	NO. OF CHILDREN NOT VACCINATED	NO. OF CASES OF POLIOMYELITIS			RATE
			NONPARALYTIC	PARALYTIC	BULBAR			NONPARALYTIC	PARALYTIC	BULBAR	
						per 100,000					*per 100,000*
Weymouth	3,063	1,251	2	0	0	159	1,812	7	3	4	772
Randolph	1,075	563	2	0	0	355	512	2	1	1†	781
Holbrook	527	181	0	0	0	0	346	1	0	0	289
Braintree	1,867	765	1	0	0	130	1,102	0	2	5	635
Quincy	4,662	1,510	1	0	1	132	1,138	8	1	3	1,054
Totals	11,194	4,270	6	0	1	164	4,910	18	7	13	774

*1 dose in 1955.
†Patient died.

*From the Department of Epidemiology, Harvard School of Public Health.

†Associate in epidemiology, Harvard School of Public Health; health officer, Town of Randolph.

‡Associate professor of epidemiology, Harvard School of Public Health; associate physician, Children's Medical Center; associate editor, *New England Journal of Medicine*.

through official channels in May, 1955, for children of the first and second grades, and several thousand eligible children were inoculated at the request of their parents; more did not avail themselves of the opportunity. When 1955 proved to be an epidemic year for Massachusetts, 5 contiguous communities a few miles south of Boston, all in Norfolk County, were selected at the close of the summer for reasons of convenience to evaluate the effectiveness of the newly available Salk vaccine. Since the improved (1955) vaccine was given only to children of the first and second grades, study of its efficacy is reasonably confined to a comparison of age-specific rates — for the children who received the vaccine and for those who did not.

Methods

The ages of patients with poliomyelitis and the dates of onset of the infection were determined from reports to boards of health, and the data were rechecked for accuracy. Also, the ages and numbers of the children in the 5 communities were obtained by school census reports, and the number of vaccinated children and their ages (as of September, 1955) from standard inoculation records; the tabulated data are given in Table 2.

In the five communities under study a total of 11,194 children made up the population six through eight years of age. Of this number 4270 (39 per cent) had received 1 inoculation and 2014* (17 per cent) either 2 or 3 inoculations by June, 1955. The remaining 4910 (44 per cent) children of comparable age had not been inoculated and may be considered a control group. No reasons are known why refusal to accept the proffered vaccine should be linked with the property of the vaccine to produce antibodies against poliomyelitis.

Results

Of 7 cases occurring among 4270 children inoculated with 1 dose (six through eight years of age) 6 were of nonparalytic and 1 was of bulbar type, as shown in Table 2. This table compares the number of cases and shows the age-specific rates observed for vaccinated and nonvaccinated children. The rate of 164 per 100,000 for clinically recognizable poliomyelitis contrasts with that of 774 per 100,000 (18 nonparalytic, 7 paralytic and 13 bulbar cases) among the 4910 nonvaccinated children of the same age group. In each of the 5 communities the age-specific rates of clinically recognizable infection were consistently much lower in vaccinated as compared with nonvaccinated children. And the difference is as striking if rates for the different clinical forms of the disease are separately examined. A single dose of this particular vaccine in the particular setting was effective as a prophylactic against paralytic poliomyelitis. On this point our findings are confirmatory of those of Pope et al.[8]

An even more important consideration was that of safety; here, the advantage of studying small communities rather than a whole state is apparent. Nothing remotely approaching an Idaho effect was

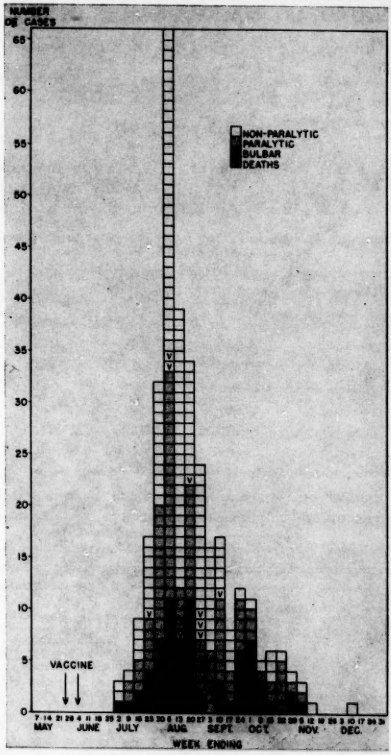


FIGURE 1. *Cases of Poliomyelitis by Severity and Dates of Onset and in Relation to May Vaccinations.*
V= *child who had received the improved (1955) vaccine.*

associated with the State-sponsored program, and the point can be demonstrated incisively and graphically (Fig. 1). No children who had been inoculated with the improved vaccine had poliomyelitis within seven and a half weeks of administration, a finding — or more precisely, the lack of a finding — most clearly demonstrated by appraisal of the epidemic profile in relation to vaccine inoculation. The earliest case (regardless of age or vaccination) did not occur until

*All were from Quincy and had participated in the 1954 field trial; 2 nonparalytic cases and 1 paralytic case occurred among these children.

June 30; nor was there any telltale accumulation of cases in families of vaccinated children in the 4 smaller communities where this possibility could be tested. Indeed, as stated previously, the vaccine was protective, and the epidemiologic findings gave every indication that the improved vaccine was safe as well as effective.

Summary

The experience of more than 4000 children six through eight years old who had received a single dose of the improved Salk vaccine in May, 1955, just before a state-wide epidemic of poliomyelitis, was compared with that of nearly 5000 children of the same age who had not received the vaccine. During the epidemic season of approximately four months the rate for paralytic and bulbar cases was ten to twenty times higher in nonvaccinated than in vaccinated children who had received 1 ml. of the newly released vaccine.

References

1. Peterson, L. J., Benson, W. W., and Graeber, F. O. Vaccination-induced poliomyelitis in Idaho: preliminary report of experience with Salk poliomyelitis vaccine. *J.A.M.A.* **159**:241-244, 1955.
2. Correspondence. Poliomyelitis Advisory Committee reports. *New Eng. J. Med.* **253**:992, 1955.
3. Pope, A. S., et al. Evaluation of poliomyelitis vaccination in Massachusetts. *New Eng. J. Med.* **254**:110-117, 1956.

HYPERLIPEMIC XANTHOMATOSIS WITH ASSOCIATED OSSEOUS GRANULOMA*

A Clinical Report

Henry J. Koch, Jr., M.D.,† and John S. Lewis, M.D.‡

New York City

THE xanthomatoses have been divided by most authors into two groups, depending on the serum cholesterol concentration.

Those exhibiting a high cholesterol in the serum are thought to result from an imbalance of cholesterol production and disposition. Secondary to the hypercholesterolemia, there may be a deposition of cholesterol in the skin, tendons, blood vessels and reticuloendothelial system. The clinical types of xanthomatoses seen in this group are usually classified according to organ-system involvement.

The second group has a normal cholesterol concentration and includes such entities as xanthoma disseminatum of the skin, osseous xanthoma and the Schüller–Christian syndrome.[1] Here, the fundamental defect is thought to be a primary granuloma with xanthoma-cell formation, reticuloendothelial proliferation and eosinophilic infiltration. Thannhauser[2] has advanced the theory that the reticulum cells and histiocytes retain the functional possibilities of embryonal fat cells and thus synthesize fat and cholesterol, which they retain within the cell and thereby gradually develop into xanthoma cells.

A third group, secondary xanthomatosis due to hyperlipemia, is included by Thannhauser[2] in his general classification of the xanthomatoses. An increase in the neutral-fat concentration is found in the serum and, according to Thannhauser, is always accompanied by hypercholesterolemia. The underlying mechanism, whether a faulty transportation of neutral fats or a faulty deposition of them, or both, is obscure. It is clinically subdivided into idiopathic and symptomatic hyperlipemia.

It is the purpose of this paper to describe a puzzling case of xanthomatosis that had characteristics found in all three of the groupings listed above and yet could not be classified in any single group.

Case Report

A 60-year-old woman was admitted to Memorial Hospital for investigation of a large osteolytic defect in the left temporal bone. From the age of 30 onward she had noted the development of yellow-orange lumps over the elbows, the forearms and the lateroposterior aspect of both legs. In addition she had noted small nodules in the extensor tendons of both hands. Five years before admission cramping pains began in both lower extremities; they occurred during exercise and were relieved by rest. Three years later, because of recurrent, acute attacks of pain in the right upper quadrant of the abdomen, a cholecystectomy was performed for cholelithiasis. About six months later, or 18 months before admission, an abscess in the left ear that responded to parenteral injections of penicillin developed. Five weeks before admission, the patient noted the sudden onset of a "roaring sound" in the left ear. X-ray study of the skull revealed a large area of destruction in the left mastoid region. A presumptive diagnosis of carcinoma of the left mastoid process, with extensive invasion of the surrounding bones, was made.

No family history of a xanthomatous disease could be elicited from the patient.

Physical examination showed a moderately obese woman whose only complaint was that of a buzzing sensation in the left ear. Examination of the head revealed no irregularities or tenderness. There was no evidence of indentation, softening or swelling in the area of bone involvement described in the x-ray report. The eyes were not remarkable. Examination of the ears showed the right external auditory canal and drum to be within normal limits whereas the left had a very narrow auditory meatus. A nontender swelling from the posterolateral portion of the canal nearly reached to the opposite side. The left ear drum could not be visualized. Examination of the nose and mouth was not remarkable. Examination of the neck was within normal limits. The chest was clear to percussion and auscultation. The heart was within normal limits. The breasts were normal. The abdomen was obese. There was no spasm or tenderness to palpation. The liver and spleen were not palpable. Vaginal and rectal examinations were not remarkable. Examination of the extremities revealed 0.6-cm. nodules in the extensor tendons of both hands and in the extensor tendons of the 2d and 4th toes, bilaterally; they were not attached to the skin. There was no ankle edema. Arterial pulsations were present in both feet. Yellow-orange masses, approximately 3 cm. in diameter, were noted on both elbows. They were movable, firm and

*From the Department of Clinical Investigation, Sloan-Kettering Institute, and the Head and Neck Division of the Department of Surgery, Memorial Center for Cancer and Allied Diseases.

†Assistant professor of medicine, Cornell University Medical School; associate, Sloan-Kettering Institute; formerly, scholar, American Cancer Society.

‡Instructor in surgery, Cornell University Medical School.

nontender. On the skin of the lower extremities there were 2 yellow, plaquelike deposits consistent with xanthoma tuberosum. The creases in the palms of both hands revealed a yellow-orange pigmentation. Neurologic examination was within normal limits.

The temperature, pulse and respirations were normal. The blood pressure was 140/90 in the right arm.

Hematologic and urinary studies were negative. The total serum protein was 6.8 gm. per 100 ml., with an albumin of 4.3 gm. The fasting blood sugar was 68 mg., the blood urea nitrogen 11.6 mg., the total serum cholesterol

FIGURE 1.

737 mg., and the free (nonesterified) cholesterol 245 mg. per 100 ml. (or 33 per cent of the total); subsequent determinations yielded values of 760 mg. and 235 mg. per 100 ml. (31 per cent) respectively. Determination of the distribution of the cholesterol in the lipoprotein fractions revealed that 7 per cent was present in the alpha-lipoprotein moiety. (This value is below the normal range for women of this age group but is of the same magnitude as reported by Barr[3] for cases of familial xanthomatosis.)

Electrocardiograms taken during the 1st hospital admission were reported as being within normal limits. Subsequent electrocardiograms during follow-up studies were always reported as normal. Radiographic examination of the skull showed an extensive destructive process involving the left mastoid process and external and middle ear and the lateral portion of the petrous ridge. The destruction extended anteriorly to the temporal bone and posteriorly to the inferior portion of the parietal and occipital bones over an area about 12 cm. in diameter (Fig. 1). A skeletal survey, conducted at the same time, revealed an area of radiolucency in the head of the right femur. X-ray studies of the lower extremities using a "soft-tissue" technic did not show an unusual degree of vessel calcification. Sternal-bone-marrow aspiration indicated normal erythropoiesis and granulopoiesis. An aspiration from the left mastoid region revealed numerous fat-laden histiocytes. Eosinophilic infiltration was noted.

The patient received 250 K.V. of x-ray therapy in a dose of 1265 r at a depth of 1 cm. to the involved portion of the left temporal bone. A single port, 12 cm. by 12 cm., was utilized. The dose was given over a 5-day period. The vertigo gradually diminished during therapy and disappeared 4 days after the final treatment was given. She was discharged from the hospital with instructions for the maintenance of a low-fat, low-calorie diet. One month later she returned with the complaint that the tinnitus, which had been absent for 6 weeks, had returned. Examination of the left ear showed an increase in the swelling to the point where it almost occluded the canal. There was no tenderness or inflammatory reaction in the swollen area. The total serum cholesterol was 510 mg. per 100 ml., with 153 mg., or 30 per cent, in the nonesterified fraction. X-ray examinations of the skull repeated 2 months after discharge showed no interval change.

Because of continued tinnitus she was readmitted to the hospital for curettage of the left mastoid region. At operation the area of bony destruction was found to consist of yellow-brown, amorphous material, granulation tissue and bone spicules. Microscopical examination revealed a foreign-body granuloma surrounding cholesterol deposits consisting of lipid histiocytes, giant cells and fibrocytic proliferation (Fig. 2). The lesion extended into the surrounding bone. Sudan III stain revealed large, red-orange droplets consistent with neutral-fat aggregates. In addition, long, needle-like crystalline clusters, which were birefringent under polarized light, were seen. Blood studies after operation showed a total lipid level of 1643 mg. per 100 ml.; the total and free forms of cholesterol were 560 and 151 mg. respectively. The patient recovered uneventfully. A total lipid level determined 1 month later was 1590 mg. per 100 ml.; the total cholesterol was 410 mg., and the nonesterified fraction was 148 mg. The urinary calcium, determined after 7 days of decreased calcium intake, was

FIGURE 2.

66 mg. per 24 hours. Because of persistent tinnitus, a 2d course of x-ray therapy was administered to the left mastoid region 5 months after operation. She received 1000 r of 1000 K.V. x-rays divided into equal doses over a 5-day period. The dose at 1 cm. was calculated to be 1100 r. The portal size was 12 x 12 cm. Two years after the 1st admission and 1 year after the 2d course of x-ray therapy, the only complaint was cramping in the lower extremities. Examination of the blood revealed continuing hyperlipemia and hypercholesterolemia. X-ray examination of the skull showed no essential change in the area of bony destruction as compared to films taken on the 1st admission.

DISCUSSION

Clinically, the skin lesions and the tendon involvement in this case can be best classified in the group

of essential xanthomatoses of the hypercholesterolemic type referred to as "xanthoma tuberosum et planum and tendon xanthoma." The nodules are "fixed" in that there is no history of disappearance with diet as seen in the secondary eruptive xanthomas of either idiopathic or secondary hyperlipemia. Since parenchymatous liver disease, diabetes and chronic pancreatitis are all excluded by either the history or the laboratory evidence, the case must be included in the idiopathic rather than in the secondary xanthomatoses. Of the laboratory findings the high serum lipid content and the elevated cholesterol levels are diagnostic evidence of hyperlipemia. The osteolytic skull lesion and, inferentially, the radiolucent area in the right femur are roentgenologically and pathologically characteristic of the lipid granuloma seen in the Schüller–Christian syndrome. This syndrome has been classified as a normocholesterolemic xanthomatosis. When the clinical and laboratory findings in this case are summarized a new syndrome emerges that has characteristics common to all three of the primary xanthomatoses, which have heretofore been considered distinct etiologic entities.

One case report[4] was found in the literature that bore a resemblance to the case described above. In that case Brehmer and Lübbers reported bony destruction in a patient with hyperlipemic xanthomatosis. However, microscopical examination of the area of bone destruction revealed a plasmacytoma rather than a lipid granuloma of the Schüller–Christian type. This patient's disease was rapidly fatal, and autopsy revealed widespread bone involvement with plasma cells of the myeloma type. It appears, therefore, that the bone lesions were not secondary to the hyperlipemic xanthomatosis in the case cited.

Although the patient described above had no evidence of coronary-artery disease either clinically or electrocardiographically, the history of intermittent claudication constitutes evidence of peripheral vascular involvement by atherosclerosis, undoubtedly secondary to the hypercholesterolemia.

Summary

A case of hyperlipemic, hypercholesterolemic xanthomatosis, with osseous lipid granuloma, is reported in detail.

References

1. Bodansky, M., and Bodansky, O. *Biochemistry of Disease.* Second edition. 1208 pp. New York: Macmillan, 1952.
2. Thannhauser, S. J. *Lipidoses: Diseases of the cellular lipid metabolism.* Edited by H. A. Christian. Second edition. 595 pp. New York: Oxford, 1950.
3. Barr, D. P. George E. Brown Memorial Lecture: some chemical factors in pathogenesis of atherosclerosis. *Circulation* **8**:641-654, 1953.
4. Brehmer, W., and Lübbers, P. Über eine generalisierte Xanthomatose mit Knochenbefall und diffuser Plasmazellwucherung in Knochenmark bei essentieller Hyperlipämie. *Virchows Arch. f. path. Anat* **318**:394-431, 1950.

AN IMPROVED "PILOT TUBE" FOR PLASTIC BLOOD CONTAINERS

A. Richardson Jones, M.B., B.S. (Lond.)*

BOSTON

MANY hemolytic transfusion reactions can be shown to have been due to human fallibility. For example, pilot or specimen tubes may be wrongly labeled; serial numbers may be misread, or blood intended for some other person may be given to the recipient. Although isoimmunization causes some serious reactions this is likely to become less of a problem as improvements are made in serologic technic. However, as blood transfusion becomes more intensively used, the opportunity for purely personal (as opposed to technologic) error increases.

The device described here is believed to be of value in preventing some of the mistakes that may occur in the use of blood-donor pilot tubes. The method, in brief, consists in utilizing the length of plastic tubing connecting the needle to the main container as the pilot tube for that particular unit of blood.

In practice, the connecting tube of a Fenwal Blood Pack is marked during manufacture with a series of small white crosses at intervals of approximately 5 cm. At the point where the tube enters the blood pack a serial number is printed, and the same number is repeated beside each cross for the whole length of the tube. The purpose of the crosses is to guide the sealing of the tube into a number of segments or "sausages" as follows.

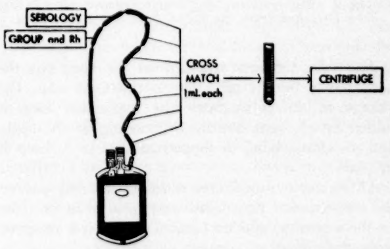


Figure 1. *Fenwal Blood Pack, with the Donor Tube Divided into Serial-Numbered Segments.*

After the donation of blood is complete, a clip is placed on the neck of the tube where it enters the bag, and the needle is withdrawn from the donor's arm, leaving the tube filled with blood. The bag and tube are then taken to the dielectric sealer, and seals are made at the places indicated by the crosses, working from the bag toward the needle. The forma-

*Research associate in pediatrics, Harvard Medical School; associate director, Blood Grouping Laboratory of Boston; executive director, Blood Bank, Children's Medical Center.

tion of the seals expresses from the needle about 2 ml. of blood, which may be collected in a dry tube for serologic tests for syphilis or discarded. It is important to permit this blood to be freely expressed, or pressure will build up in the plastic tube, preventing proper sealing. It is also important to carry out the sealing operation within an hour of blood collection, or clot retraction may give rise to uneven distribution of cells and serum in each segment. The bag and tube now have the appearance shown in Figure 1.

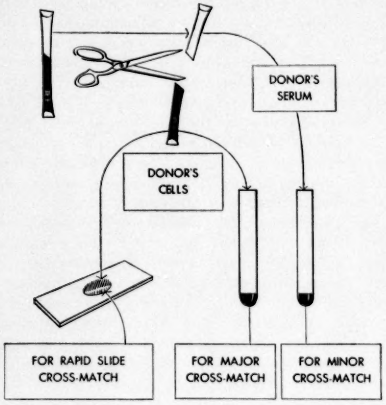


FIGURE 2. *Manipulation of a Single Segment after It Has Been Detached from the Blood Pack and Centrifuged.*

The tube remains attached to the bag, but the needle may be cut off close to the final seal. For storage in the refrigerator the segmented tube is folded into a neat bundle by bending at the seals, and an elastic band is slipped around it to keep it in place.

All serologic procedures normally carried out on the conventional pilot tubes may now be undertaken on the segments, and no further specimen is required from the donor.

Each segment contains a little under 1 ml. of clotted blood and is clearly labeled with a serial number. The blood in the segment is obviously serologically identical to the blood in the bag to which it is joined, and sterility of the specimens is assured.

The use of the segments is shown in Figure 2. If, for example, it is desired to carry out a compatibility test on the bag, the distal segment of tube is snipped through the middle of the seal and placed, with the serial number downward, in a test tube, 10 by 70 mm., which is filled with saline solution as a hydrostatic cushion. The tube is then centrifuged to separate cells and serum. After centrifugation the segment is drawn from the tube with forceps and cut through the serum-cell interface. Each half-segment now becomes a miniature dropper, and at least 2 generous drops of serum may be squeezed from the upper half for the "minor" crossmatch. The lower half contains packed cells in the clot, and from this part, cells may be readily extracted to make a saline suspension or transferred directly to the recipient's serum on an applicator stick for a high-protein "major" crossmatch, or they may be squeezed directly on to a warmed slide as a heavy suspension for a "rapid-slide" major crossmatch. The serial number of the segment is so disposed that it is not cut through when cells and serum are separated, and the cell-containing part may be retained as a permanent record of the serial number of the donor used in the test.

The nine segments into which each connecting tube is divided provide material for an adequate number of compatibility tests, as well as one segment each for micro-Hinton test and a check of the donor's group and Rh type.

SUMMARY

By forming pre-numbered segments, the plastic connecting tube of a Fenwal Blood Pack may be used as a donor pilot tube. This method provides obvious advantages for ensuring the identity and sterility of the specimens. It is believed to provide some additional means of safety in compatibility tests.

I am indebted to the Fenwal Company for its co-operation in developing the system of numbering the plastic segments and in providing prototype blood packs.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42341

PRESENTATION OF CASE

First admission. A forty-one-year-old Negress was admitted to the hospital because of pain in the chest.

Thirteen months previously she noted dyspnea on exertion and paroxysmal nocturnal dyspnea. There was an episode of crushing pain in the left side of the chest that radiated down the left arm. Physical examination showed an obese woman who weighed 206 pounds. The heart was slightly enlarged to the left. A Grade 2, decrescendo early diastolic aortic murmur that was loudest in the third left intercostal space and a Grade 2, apical, systolic murmur were audible. The mitral first sound was slightly accentuated. There was no peripheral edema. The blood pressure was 140 systolic, 60 diastolic. X-ray films of the chest showed slight enlargement of the heart to the left. An electrocardiogram was normal. Digitalis therapy was begun. Three months later there was a severe upper respiratory infection, the temperature rising to 101.4°F. X-ray films of the chest showed no change. Five months before entry there were episodes of palpitation, dyspnea and coughing that were relieved when the patient was in an upright position. There was no exertional dyspnea or swelling of the ankles. Night sweats were noted. The weight was 170 pounds. Examination of the heart showed no change. X-ray films of the chest demonstrated a further increase in the size of the heart, as well as increased pulmonary congestion and pleural fluid bilaterally. An electrocardiogram showed a pattern consistent with left ventricular hypertrophy and the effect of digitalis. With continuation of digitalis and Mercuhydrin and a low-salt diet the dyspnea was somewhat relieved. One month later there was increased dyspnea with orthopnea, malaise, fatigue, chilliness, cough and an episode of pain in the anterior portion of the chest. The temperature ranged between normal and 101.8° F. The weight was 147 pounds. The veins of the neck were distended when the patient was raised to an angle of 30°. Examination of the heart revealed a Grade 3, apical, systolic murmur, a Grade 2, aortic, systolic murmur and a Grade 3, decrescendo, aortic, diastolic murmur that was transmitted along the left sternal border. The blood pressure was 140 systolic, 40 to 0 diastolic. Examination of the blood revealed a hemoglobin of 10.3 gm. per 100 ml. and a white-cell count of 8200. X-ray films of the chest showed pulmonary congestion without further cardiac enlargement. An electrocardiogram showed no change except for diminished amplitude of the QRS interval in the lateral chest leads. Three months before admission there were episodes of nausea and vomiting and a cough productive of blood-streaked sputum. One month later the hemoglobin was 9.7 gm. per 100 ml. and the reticulocyte count was 2.3 per cent. The serum iron was 40 microgm. per 100 ml. Iron therapy was begun. During the month before entry there were episodes of palpitation, increasing dyspnea, paroxysmal nocturnal dyspnea, anorexia, a cough productive of blood-tinged sputum, severe frontoparietal headaches, night sweats, weakness and a further loss in weight to 118 pounds. There were also episodes of sharp, stabbing, pleuritic pain in the lower right side of the chest that radiated to the right side of the neck and to the groin. A shaking chill and fever were noted.

Twenty years previously the patient was treated for secondary syphilis with arsenicals and bismuth. She also had gonorrhea. Examination of the heart at that time revealed a faint mitral systolic murmur. Subsequent blood Hinton tests were negative. She had pneumonia when she was nineteen years of age. Over a period of many years numerous abscesses of the breasts, buttocks and thighs were incised and drained. Four years previously a right salpingectomy and a left salpingo-oöphorectomy were performed at another hospital because of acute and chronic salpingitis. The fasting blood sugar was 87 mg. thirteen months before admission and 117 mg. and 109 mg. per 100 ml. nine months before admission. The patient's mother had died of diabetes mellitus.

Physical examination revealed a debilitated woman. There were rapid, shallow respirations and decreased respiratory excursions, with splinting of the right side of the chest. The veins of the neck were not distended. Dullness, almost absent breath sounds and crackling inspiratory and expiratory rales were noted over the right-lower-lung field. Examination of the heart showed the left border of cardiac dullness to extend to the anterior axillary line. There was a normal sinus rhythm at a rate of 132. The first mitral sound was loud; the pulmonic second sound was louder than the aortic. A marked apical systolic thrill was noted. A Grade 3, decrescendo, aortic, diastolic murmur that was transmitted along

the left sternal border and a harsh, Grade 4, apical, systolic murmur were audible. Examination of the abdomen showed guarding of the right side and marked tenderness over the liver, which was felt 3 fingerbreadths below the right costal margin. The spleen was not palpable. The right pupil was irregular, but both pupils were reactive. A collapsing peripheral pulse was noted.

The temperature was 104.2°F., the pulse 132, and the respirations 50. The blood pressure was 120 systolic, 20 to 0 diastolic.

The urine gave a + + + test for albumin and a green test for sugar. Examination of the blood revealed a hemoglobin of 11.5 gm. per 100 ml. and a white-cell count of 24,000, with 87 per cent neutrophils. The nonprotein nitrogen was 37 mg., the bilirubin 1.2 mg., the total protein 7.4 gm., the albumin 2.9 gm., the globulin 4.5 gm., and the fasting blood sugar 104 mg. per 100 ml. The sodium was 128 milliequiv., the potassium 4.6 milliequiv., and the chloride 86 milliequiv. per liter. The serum electrophoretic pattern showed a decrease in the albumin and an increase in the gamma globulin. The electrophoretic pattern of the hemoglobin was normal. Cultures of the blood and the sputum grew out abundant pneumococci. Examination of the sputum for acid-fast bacilli and cytologic examination for malignant cells were negative. The tuberculin test (PPD) was positive. X-ray films of the chest demonstrated an area of increased density obscuring the right-lower-lung field, a right-sided pleural effusion and generalized cardiac enlargement; the aortic arch, which was diminutive, showed minimal calcification. An electrocardiogram showed nonspecific abnormalities of the T waves. A lumbar puncture yielded clear cerebrospinal fluid under a pressure equivalent to 130 mm. of water; it contained 8 mononuclear cells per cubic millimeter; the total protein was 20 mg. per 100 ml., and the gold-sol curve 0001100000; the Hinton test was negative.

Antibiotic therapy was given. The temperature rose to 105°F. on the first hospital day and ranged between 100.2 and 103.4°F. during the next three days. Thereafter, it gradually fell to a range between 99.2 and 101°F. There was an improvement in symptoms. The white-cell count fell to normal. Subsequent cultures of the blood were negative, and cultures of the sputum grew out abundant colonies of coliform bacilli and moderate colonies of alpha-hemolytic streptococci. X-ray films of the chest on the fifth hospital day showed clearing of the consolidation of the right lower lobe, with some residuum in the apical and posterior basal segments; the previously noted pleural effusion showed no change; the heart appeared slightly smaller and there was a suggestion of fullness in the region of the left atrium (Fig. 1). Fluoroscopic examination two days later showed moderate cardiac enlargement with normal pulsations; the previously noted residual densities were still present. On the eleventh hospital day a thoracentesis on the right yielded 35 ml. of straw-colored fluid that contained 6000 red cells and 6000 white cells, with 40 per cent neutrophils, 40 per cent lymphocytes and 20 per cent epithelial cells, per cubic millimeter; a culture showed no growth; cytologic examination for malignant cells was negative. X-ray films of the chest on the sixteenth hospital day still showed increased markings in the right-lower-lung field; the density in the region of the major fissure appeared somewhat smaller and less opaque. No appreciable change was seen six days later. An intravenous pyelogram showed slight enlargement of the right kidney; the contrast substance appeared promptly and in good concentration bilaterally. An upper gastrointestinal series was normal. An electrocardiogram on the twenty-sixth hospital day showed slight depression and sagging of the ST segments with low diphasic T waves in Leads 2, 3, aVF, V_4 and V_5; the T waves were low in Leads 1, aVL and V_3 and inverted in Lead V_6; there were tall R waves in

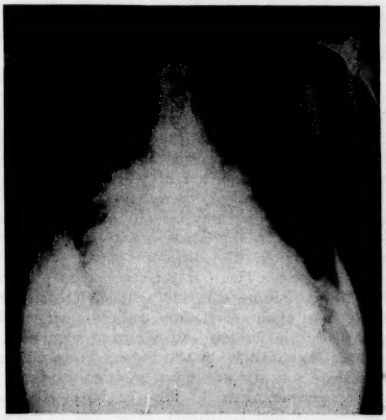


FIGURE 1. *Roentgenogram of the Chest Taken Five Days after Admission, Showing Cardiac Enlargement, Fluid in the Right Pleural Space and Patchy Consolidation in the Lower Half of the Right Lung.*

Leads V_4 and V_5. Films of the chest on the thirty-second hospital day demonstrated an increase in the size of the heart and a slight increase in the fluid in the right pleural space; there was an increase in the area of consolidation that obscured the medial portion of the right leaf of the diaphragm.

On the thirty-third hospital day there was a sudden episode of sharp pleuritic pain in the anterior portion of the chest that radiated to the back and was associated with increased dyspnea and a nonproductive cough. There was distention of the veins of the neck. Examination of the chest showed dullness and

diminished breath sounds at the right-lung base. There was no tenderness of the calves. The temperature was normal, the pulse 96, and the respirations 40. The blood pressure was 100 systolic, 0 diastolic. An electrocardiogram showed sagging of the ST segments with prominent R waves in Leads 2, 3, aVF and V_4 through V_6; the P waves were somewhat prominent, and the T waves were low. Four days later a bilateral superficial-femoral-vein ligation was performed; no thrombi were found. Three days later x-ray films of the chest showed no appreciable change. The patient was discharged afebrile on the sixth postoperative day.

Final admission (two months later). In the interval she continued to be dyspneic. Four weeks before entry there was an episode of pleuritic pain in the left side of the chest anteriorly, as well as transient tinnitus in the left ear, with vertigo and numbness of the left side of the mouth. Two weeks later she began to cough up considerable amounts of blood in the sputum and complained of pain in the right side of the pelvis and groin. Gradually increasing pitting edema of the ankles was noted.

Physical examination showed no distention of the veins of the neck. Dullness and diminished breath sounds were noted over the right-lung base. Over the anterior and lateral portions of the left side of the chest diminished breath sounds and a rough pleural friction rub were audible. The aortic second sound was not heard. The murmurs were as previously noted. The edge of the liver was percussed 4 fingerbreadths below the right costal margin. There was + + pitting edema of the ankles.

The temperature was 99.8°F., the pulse 90, and the respirations 24. The blood pressure was 130 systolic, 40 to 0 diastolic.

The urine gave a green test for sugar. Examination of the blood revealed a hemoglobin of 9 gm. per 100 ml. and a white-cell count of 8500. A culture of the sputum grew out moderate colonies of pneumococci. X-ray films of the chest demonstrated some residual pleural thickening in the right hemithorax; there was a triangular area of homogeneous density in the axillary portion of the left upper lobe; the heart was enlarged in the region of the left ventricle and atrium. An electrocardiogram showed a normal sinus rhythm at a rate of 80; the PR and QRS intervals were 0.22 and 0.09 seconds, respectively; there was slurring of the ST segments, with low to diphasic T waves in Leads 1, 2, 3 and aVF; the ST segments were depressed and the T waves were inverted to diphasic in Leads V_4 through V_6; there were prominent R waves in Lead 5; the QT interval was at the upper limits of normal.

Anticoagulants and penicillin therapy were given. The patient continued to cough up blood-tinged sputum. There was progressive dyspnea and tachypnea, with respirations ranging between 22 and 60. The temperature ranged between normal and 100.4° F. An electrocardiogram on the eighth hospital day showed a slight decrease in the QT interval and persistent diffuse changes in the ST segments and the T waves. Two days later a loud, rough friction rub was audible in the right axilla. The edge of the liver, which was tender, was felt 5 fingerbreadths below the right costal margin. The tip of the spleen was palpable. She gradually became unresponsive and died on the eleventh hospital day.

Differential Diagnosis

Dr. Benjamin Castleman: This case was supposed to be discussed by a cardiologist from a neighboring hospital. Through some mix-up, he thought he had been invited for next week and is not here. I have just asked Dr. Friedlich to discuss the case without having had the opportunity to study it beforehand. That is the way Dr. Richard Cabot used to discuss these cases in the early days of these exercises.

Dr. Allan L. Friedlich*: At the time of the first admission this patient had lost a great deal more weight than one could attribute to a strict, low-sodium diet and poor nutrition alone. The exertional and paroxysmal nocturnal dyspnea, together with the murmurs described thirteen months before the first admission, raise the question of slight aortic regurgitation on the basis of syphilis or rheumatic valvular disease, perhaps with mitral regurgitation. In addition, there was not free aortic regurgitation at that time because the diastolic blood pressure was 60. At that time the electrocardiogram was normal.

Eight months later the patient had obvious evidence of congestive heart failure in that there was an increase in the size of the heart, increased pulmonary congestion and pleural fluid bilaterally. The electrocardiogram, which previously had been normal, now gave evidence of hypertrophy of the left ventricle. A month later the murmurs of both aortic and mitral regurgitation had increased in intensity, as a result either of dilatation of the heart or of additional damage to the valves. At any rate there was an important increase in the degree of aortic regurgitation, for the diastolic pressure was now 40 to 0.

The night sweats, together with the evidence of valvular lesions and the febrile episodes before admission, should make one suspect subacute bacterial endocarditis. The blood-streaked sputum raises the question of pulmonary infection or infarction, although this could have resulted from severe congestive heart failure alone. The fact that the neck veins were not distended at the time of the first admission is against the nausea and vomiting occurring as a result of congestion of the liver.

*Assistant physician, Massachusetts General Hospital.

The high white-cell count on admission indicates that something in addition to congestive heart failure and a subacute bacterial endocarditis was present — either pneumonia or pulmonary infarction. The high percentage of neutrophils is in favor of infection. Moreover, the cultures of the sputum grew pneumococci. Therefore, I must decide whether the patient had subacute bacterial endocarditis, extending over a long period, with a superimposed pneumonia and pneumococcal bacteremia, or whether she had an acute pneumococcal endocarditis over the whole period, which would be much less common.

During the first admission ligation of the leg veins was carried out so that the physicians caring for her thought that she had a pulmonary embolus. During the final admission, the numbness of the face and tinnitus may have indicated an embolus to the central nervous system.

May I see the x-ray films? I am surprised to hear that there was a diminutive aortic arch in the presence of free aortic regurgitation.

DR. PAUL M. G. ST. AUBIN: The films taken after the first admission show generalized enlargement of the heart and an area of density in the right-lower-lung field. Five days later there has been a decided clearing of the density in that portion of the lung, revealing what appears to be pleural fluid and an area of consolidation, which is probably in the right lower lobe posteriorly (Fig. 1). Aerated bronchi are seen within this area of consolidation, a finding that is diagnostic of pneumonia. An area of ill defined density, 4 cm. in diameter, in the right-middle-lung field is suggestive of localized pulmonary edema. The arch of the aorta is better seen on this later film than on the admission film, and both the arch and the descending portion of the thoracic aorta are normal in appearance.

DR. FRIEDLICH: Would you say the aorta is small? Is the left atrium enlarged?

DR. ST. AUBIN: The aorta appears normal. The left atrium is enlarged; it is seen in the lateral projection and in the right anterior oblique projection, where it produced a localized impression on the barium-filled esophagus. In the posteroanterior projection there is a slight elevation of the left main bronchus, which indicates an enlargement of the left atrium.

DR. FRIEDLICH: Incidentally, did the calcification in the aorta involve chiefly the ascending aorta?

DR. ST. AUBIN: I cannot see any calcification in the ascending aorta; there is a small amount visible in the arch.

DR. FRIEDLICH: If the ascending aorta was calcified that would swing me strongly toward syphilitic heart disease.

There was one episode that was clearly pneumonia, with bacteremia, which apparently cleared, and blood cultures were negative thereafter. The several episodes in the last few months of the patient's life, I think, were most probably the result of pulmonary infarction. The fact that they continued to occur after bilateral superficial-femoral-vein ligation has unfortunately been seen in the past. Unrecognized sources of pulmonary bleeding, I think, are unlikely because the films demonstrated relatively clear lung fields.

I think that the considerable weight loss early in the course of the illness and the change in the auscultatory findings are important. They make me suspect that the patient had subacute bacterial endocarditis of long duration, engrafted most probably on syphilitic heart disease, although I cannot be certain that she did not have rheumatic aortic regurgitation with mitral regurgitation as well. In the x-ray films there was nothing suggestive of dissection of the aorta with rupture into a bronchus to account for the gross hemoptysis leading to the final admission. The pain occurred a considerable time before the first admission. It would be unusual for an aortic dissection to continue so long and to be associated with an aorta that appeared on x-ray examination to be of normal or small size. I think I shall choose long-standing subacute bacterial endocarditis engrafted on syphilitic heart disease, with pneumonia, bacteremia and pulmonary infarction.

DR. CASTLEMAN: Do you mean endocarditis involving the aortic valve alone? There was a Grade 3, systolic thrill at the apex.

DR. FRIEDLICH: I think it could have involved the mitral valve too.

DR. CASTLEMAN: How do you account for the Grade 3, systolic thrill at the apex?

DR. FRIEDLICH: Such a thrill may have been present as a result of increasing damage to the mitral valve from infection; sometimes, it may be due to a dilated mitral-valve ring seen in patients with severe left ventricular failure. In such a case it often becomes faint or disappears if the congestive heart failure is brought under control.

DR. CASTLEMAN: So you believe that the patient had fundamentally syphilitic aortic regurgitation on which a bacterial endocarditis was engrafted?

DR. FRIEDLICH: Yes, with functional mitral regurgitation. The other possibility is rheumatic heart disease with infection of both valves. Since I know that she had previous syphilis, I favor syphilitic heart disease. Slight aortic regurgitation is the valvular defect that is most susceptible to this infection.

DR. JACOB LERMAN: Do you explain the large left atrium by a dilated heart, or do you think it is evidence of mitral stenosis?

DR. FRIEDLICH: That would be in favor of mitral stenosis or regurgitation. Usually, when there is functional regurgitation of that degree, the heart is so large that selective enlargement of the left atrium cannot be seen in the x-ray films. It is a decided point in favor of organic disease of the mitral valve.

DR. ST. AUBIN: That is true.

DR. WALTER F. JONES, JR.: Do you think that the mitral murmur that was present twenty years before admission was a clue to rheumatic heart disease?

DR. FRIEDLICH: That is a possibility, but it was faint and hence of dubious importance.

A PHYSICIAN: From where would the pulmonary infarcts have come?

DR. FRIEDLICH: The patient is not likely to have had infection on the right side of the heart, itself, with septic pulmonary infarction from that origin. Statistically, the chances of their coming from the leg veins, even after ligation of the superficial femoral veins, is a better bet.

DR. LERMAN: The patient also had pelvic infection for a long time and a pelvic operation. They could have come from the pelvic veins.

CLINICAL DIAGNOSES

Pulmonary emboli, recurrent.
Rheumatic heart disease, with aortic and mitral regurgitation.
?Syphilis, tertiary.
?Nutritional cirrhosis.
Diabetes mellitus, mild.

DR. ALLAN L. FRIEDLICH'S DIAGNOSES

Subacute bacterial endocarditis superimposed on syphilitic aortic valvulitis.
Syphilitic heart disease, with aortic regurgitation and functional mitral regurgitation.
Pulmonary emboli.

ANATOMICAL DIAGNOSES

Subacute bacterial endocarditis of mitral and aortic valves.
Mycotic aneurysm, aortic cusp of mitral valve, with rupture.
Pneumonitis, hemorrhagic, right upper and left lower lobes.
Chronic passive congestion and central necrosis of liver, marked.
Recent infarcts of spleen and heart.
Healed infarcts of kidney.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Thank you very much for taking on this case on the spur of the moment.

The heart was large and dilated. Half of two of the cusps and a part of the third cusp of the aortic valve were eaten away by a bacterial endocarditis (Fig. 2). There was no evidence of syphilis in the aorta above the valve; it was smooth and free of arteriosclerosis. There was no separation of the aortic cusps at the commissures, such as that seen with a syphilitic aortitis involving the aortic valve, and practically no interadherence between cusps; the cusps themselves were not thickened like those in rheumatic valvulitis. Thus, I am unable to say that there was any underlying rheumatic or syphilitic involvement in the aortic valve. On the aortic leaflet of the mitral valve was a large vegetation. Contiguous to the vegetation was a perforated mycotic aneurysm of the leaflet (Fig. 2). The other leaflet of the mitral valve looked normal. The process must have existed a long time, for the perforation was not very ragged, and there was still active endocarditis,

FIGURE 2. *Photograph of the Heart and Aortic Valve. The arrows point to the perforated mycotic aneurysm.*

some of which was present on the chordae tendineae. The chordae tendineae themselves were normal, indicating no previous rheumatic infection.

In reconstructing this sequence of events, I do not know how to account for the first episode thirteen months before admission. Ten months before admission, when the patient had pneumonia, I think she had a bacterial endocarditis that involved the aortic valve and the aortic leaflet of the mitral valve, the latter forming a mycotic aneurysm. Seven or eight months before admission, or at least when she began to have very severe right-sided cardiac failure with distended neck veins and hemoptysis, the aneurysm perforated. By the time she was admitted to the hospital, when she had the Grade 3 thrill, I believe that she had already had the perforation of the mitral cusp, which produced marked regurgitation of the mitral valve. The bacterial endocarditis was partially helped by the antibiotics; although we were not able to find any organisms at the time of autopsy, there was still activity as a result of the continued bacterial endocarditis. A section of the aorta gave no evidence of syphilis, so I suppose that it was a bacterial endocarditis engrafted on a normal valve. If there was evidence of syphilis it must have been very slight. Certainly, the aorta itself did not show any. The lesions in the lungs were not infarcts; they were areas of pneumonia with organization and a great deal of hemorrhage.

DR. FRIEDLICH: Do you think it was pneumococcal endocarditis? Pneumococci more commonly en-

graft on a normal valve. On the other hand, it would be very rare for endocarditis due to this organism to go on such a long time before death.

DR. CASTLEMAN: I suppose that it could be present for this period. The patient did not get any antibiotics until she came into the hospital. There is evidence that the endocarditis existed for a long time because there were healed infarcts in the kidney and evidence that it was still active, because there were acute infarcts in the spleen. One small miliary infarct that was healing was present in the myocardium. Three fourths of each lobule of the liver was necrotic and congested.

CASE 42342

PRESENTATION OF CASE

A thirty-four-year-old, divorced, para 2, gravida 2, waitress entered the hospital because of menorrhagia.

For three weeks before admission she had noted persistent vaginal bleeding, with passage of clots requiring six or seven pads daily, as well as weakness and dizziness. The last menstrual period occurred six weeks before entry. The periods were regular, occurring every twenty-eight to thirty days, lasting five to seven days and requiring four pads daily. There were occasional menstrual cramps.

An appendectomy was performed twenty years previously. Four years before admission an exploratory laparotomy was performed at another hospital because of peritonitis of unknown etiology. A cervical polyp was also removed.

Physical examination showed a well nourished woman in no distress. A healed right-lower-quadrant abdominal incision was present. Pelvic examination revealed a normal cervix; the uterus, which was small and mobile, lay anteriorly; the left ovary was normal, and the right ovary was not identified; a nontender cystic mass measuring 12 cm. in diameter was lodged in the pelvic inlet and bulged the cul-de-sac anteriorly.

The temperature was 98.2°F., the pulse 80, and the respirations 20. The blood pressure was 120 systolic, 80 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 12.2 gm. per 100 ml., with a white-cell count of 9200. The platelets were normal. The serum nonprotein nitrogen was 24 mg., and the fasting blood sugar was 85 mg. per 100 ml. The prothrombin content was 60 per cent, and the bleeding time normal. The blood Hinton test was negative. Proctoscopic examination up to 13 cm. was negative. Uterine curettage showed proliferative endometrium.

On the third hospital day an operation was performed.

DIFFERENTIAL DIAGNOSES

DR. HERMES C. GRILLO*: The problem presented by this case is that of the relation of an otherwise asymptomatic pelvic mass to menorrhagia from a grossly normal uterus, with proliferative endometrium. Without the mass there would be little to say beyond applying the descriptive term, functional uterine bleeding of estrogenic type.

Let us now sort out the evidence and comment on a few of the possibilities suggested by the evidence. The menstrual periods were regular, not excessive in flow and accompanied only by occasional cramps. The bleeding began three weeks after an allegedly normal period. This was, therefore, the first episode of bleeding. With the curettage showing proliferative endometrium the patient evidently did not ovulate after the last "normal" period. Whether any number of the presumably normal prior periods were anovulatory is impossible to state. The absence of menstrual cramps may be noted as evidence against endometriosis, if we are tempted to describe this as menorrhagia associated with a chocolate cyst of the right ovary. In addition she had no other pelvic pain. Pelvic pain, especially worsened at menses, is characteristic of endometriosis.

Appendectomy was done twenty years before admission, so that the peritonitis four years before admission was, in a woman of thirty-four, very probably related to adnexal disease. From the later information that she had been explored in the right lower quadrant (the previous appendectomy incision I suppose, being excised) we may assume that the peritonitis was localized by the surgeon to the lower abdomen. I must also assume that this diagnosis seems justified in retrospective history since it is notoriously misleading to accept the simple statement of many patients about previous surgical procedures and diagnoses. In a woman of this age pelvic inflammatory disease would be a prime possibility. The sociologic data are consistent, but must not be overweighted without more knowledge of the patient. The later description of a pelvic mass, possibly derived from the right adnexa since the right ovary could not be felt and the left was normal, gives me pause in the light of the previous operation. However, depending on the state of the disease, a diseased tube or tuboovarian mass might not have been excised at prior surgery, or else only a tubal mass excised and the ovary left in place. Often, when a diseased tube alone is excised, the ovary later becomes involved in an abscess or inflammatory cyst.

Another possibility is rupture of an ovarian endometrioma four years before entry. The age and pregnancy history, as well as the previously mentioned painless menses, are against this.

If we assume that the current mass was of the right adnexa, we also rule out a prior "peritonitis"

*Assistant in surgery, Massachusetts General Hospital.

due to infarction of a twisted ovarian cyst, since it would have been excised at the time of operation.

Physical examination showed a normal cervix and a small, mobile uterus, anteriorly. If any further evidence is needed against endometriosis, we might note the absence of fixation of the lower portion of the uterus, the absence of nodules in the uterosacral ligaments or cul-de-sac and the absence of tenderness or pain on pelvic examination.

What other masses are associated with abnormal uterine bleeding? Functional ovarian tumors must be considered, and, in the light of the information available, only those secreting estrogens. Granulosa-cell tumors of the ovary cause irregular uterine bleeding by continuous estrogen stimulus, although amenorrhea may often be a preceding phase. They occur in a wide age distribution. But several other points are against this diagnosis: the tumor was cystic, and granulosa-cell tumors are usually solid; in the presence of these tumors the uterus is frequently enlarged and often contains fibroids. Neither was present here. The history of menstrual irregularity was short for such a large tumor if it was a granulosa-cell tumor.

The vital signs were normal, and this is evidence against a true exacerbation of pelvic inflammatory disease. However, menstrual disorders, caused presumably by poorly understood ovarian dysfunction from chronic "burnt out" pelvic inflammatory disease, occur. In this case there would be no expectation of rise in temperature, or of a locally tender mass. The uterus may also remain surprisingly mobile in such a state, the degree of scarring being quite variable. The history of previous probable pelvic peritonitis is consistent, of course, with this diagnosis.

The laboratory work is of significance in telling us, along with vital signs and clinical data, that the bleeding had not been massive. The platelets were normal, and the bleeding time was also normal. This avoids a discussion of idiopathic thrombocytopenia, which may often manifest itself first in menorrhagia.

The negative proctoscopy up to 13 cm. merely helps assure us that the mass was not an intrinsic large-bowel mass, although a colonic mesenteric mass is not, of course, excluded.

I have already alluded to the proliferative endometrium on several occasions. This seems to eliminate the need for discussion of conditions with bleeding and masses in which the endometrium would be secretory or would show a decidual reaction.

I can best tie the history and findings together with a diagnosis of functional uterine bleeding associated with old pelvic inflammatory disease. A variant on this diagnosis in which the relation between mass and bleeding is not better explained and may actually be unrelated — hence breaking a fundamental pedagogic rule — is the diagnosis of functional uterine bleeding and noninflammatory cyst of the right ovary. However, if this was the case, there are many other unrelated masses that must be discussed, including other ovarian tumors, retroperitoneal tumors, mesenteric cysts and old pelvic foreign bodies, and the exercise would hence be pointless.

Therefore, my diagnosis is functional uterine bleeding caused by old pelvic inflammatory disease, producing the mass.

DR. LEONARD ATKINS: Dr. Wheeler, will you tell us the impression on the ward and what was found at operation?

DR. C. G. WHEELER: The house staff on the ward believed that the prime problem was one of a large ovarian cyst, as Dr. Grillo has deduced. We kept in mind the old history of pelvic inflammatory disease but believed that the pelvic mass and bleeding were probably not primarily due to pelvic inflammatory disease.

CLINICAL DIAGNOSES

Large ovarian cyst.
Abnormal uterine bleeding.

DR. HERMES C. GRILLO'S DIAGNOSIS

Functional uterine bleeding, associated with old pelvic inflammatory disease.

ANATOMICAL DIAGNOSES

Salpingitis, acute and chronic, bilateral, with pyosalpinx, right.
Follicular cysts, ovarian, bilateral.

PATHOLOGICAL DISCUSSION

DR. WHEELER: At laparotomy the right salpinx was dilated, not inflamed, lay in the cul-de-sac and was filled with greenish pus, which on cultures grew no organisms. Both adnexa were bound down by moderate adhesions; however, the adnexa and uterus were easily freed and mobilized in the usual manner. The small ovarian cysts were quite insignificant but probably represented sufficient estrogen reservoir to produce proliferative endometrium and account for the nonovulatory bleeding.

DR. ATKINS: The specimen that we received consisted of the uterus and both adnexa. The diameter of the right fallopian tube, which was dilated with purulent material, was about twice the normal size and apparently was the mass lodged in the pelvic outlet. Microscopically, both tubes showed a marked acute and chronic inflammatory reaction. Follicular cysts, the largest measuring 1.6 cm. in diameter, were found in both ovaries.

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A COMMON FELLOWSHIP

MORE than five years ago the *Journal* commented editorially on facts related to membership in the Massachusetts Medical Society that brought out the failure of many physicians in specialized types of work to apply for fellowship.* Commenting on this failure did not then and does not now constitute an indictment of any individuals or a criticism except insofar as a failure to meet fully the expanding activities of the profession may give rise to a criticism of organized medicine. The fact is that many full-time teachers, investigators and administrators were not then and are not now fellows of the Society and no particular effort is being made to draw them into the fold. The Society appears to have little to offer them in their relative isolation, nor is it conscious of any great loss in their nonmembership. Both may presumably be the losers.

The reasons for joining geographically and politically defined medical organizations — one's state and district societies — go back to the original concept of them all — like that of Massachusetts, "medical institutions . . . helpful in maintaining the health and hence the happiness of the citizens of the Commonwealth." At the time of the founding of the Society the function of the physician in promoting health and happiness was through private practice, and to the improvement of such practice and its practitioners the Society was devoted. The reasons for joining, therefore, were and are to share the common interests that practitioners enjoy, — the majority of the Society's activities being slanted toward private practice, — and such tangible advantages as eligibility for hospital privileges, inclusion in group insurance plans and so forth.

These are the important incentives for joining the group — the advantages of a co-operative educational and mutually protective association of those engaged in a common calling. There are also reasons why those similarly trained but differently occupied should wish *not* to join the group, other than lack of an incentive to become part of a medical organization the main interests of which are centered away from their fields. Among these are the requirement of a license to practice — a definite hindrance for those who have no intention of practicing; the requirement of an examination, quite possibly on unfamiliar subjects; the payment of a not inconsiderable annual fee; and the obvious lack of any obvious advantage to the anatomist, the biologic chemist, the physiologist or the medical-school dean.

Even a hundred years ago almost all anatomists found it necessary, as did John Hunter, to earn that guinea in practice in order to maintain strength for their anatomizing, and within the half century many a medical-school dean has had to administer his educational institution between patients. State-medical-

*Editorial. Common goal. *New Eng. J. Med.* **244**:772, 1951.

society membership was a *sine qua non* for these dispensers of the omega as well as cultivators of the alpha of medical service, and it was natural that they should take leading parts in the genteel medical debating societies of their day.

The science of medicine, however, has developed as its art has declined. Its bases have broadened, and the person who discovers a new form of medical service is unlikely to be in the same field as those who either teach it or deliver it. The services of the medical society have also become complicated, as a list of its committees and their activities will attest, but they are still directed largely to the practitioner and his problems and less directly to the patient and his problems, and at times a hint of trade unionism may seem to be part of the over-all picture.

This being the case it is not utterly absurd to suggest again, as was suggested in 1951, that the sturdy but diverging branches of the profession be brought closer together. Even as the Society may find services that it can perform for the laboratory toiler or the administrator of large affairs, it may also find that the dean of the medical school or the adventurer in pharmacology can add luster to its rolls, contributing learning to its discussions and wise counsel in its deliberations.

As was indicated in 1951, divergences should be recognized and not ignored:

> Fences should be torn down and not erected; the exchange of ideas should be facilitated and not impeded. Perhaps, in view of the diversity of the activities of modern medicine, the rules should be changed to give more nearly equal opportunities to the various nonpracticing specialties.

ADENOVIRUSES

EVER since Rowe and his co-workers[1] at the National Institutes of Health described the isolation of cytopathogenic agents from tissue cultures of surgically removed adenoids there have been a large number of similar and related strains of viruses isolated in cultures of various human and monkey tissues by a number of workers and from a variety of clinical syndromes involving the respiratory tract. In their original description, these workers proposed the term "adenoid degenerating agent," abbreviated as "A.D. agent." Hilleman and Werner,[2] who independently reported the isolation of viral strains during an epidemic of acute respiratory disease and pneumonitis in Army recruits, called their strains *respiratory-illness (RI) agents.* When further data showed all these viruses to be related to clinical syndromes that most frequently involved the respiratory tract and conjunctivas, the workers at the National Institutes of Health[3] proposed the term *adenoidal-pharyngeal-conjunctival (APC)* agents or viruses as the group name.

Recognizing the desirability of standardizing the terminology in this important area of laboratory and clinical research, representatives of the early investigators in the field and a number of prominent and interested investigators met recently to discuss this problem. They agreed on the term *adenovirus group* as one that satisfies the accepted criteria for nomenclature.[4] This term suggests a characteristic involvement of lymphadenoid tissue as well as the tissue of the first reported isolation. For the present, members of this group would be indicated by serotype numbers in accordance with the classification of Huebner and his associates.[3,4] Thus far, 12 serologically distinct types have been established from human and 2 from simian materials.

The viruses at present included in this group are described as having the following characteristics: they produce acute infection of respiratory and ocular mucous membranes with associated follicular enlargement of submucous lymphadenoid tissue in these areas and also of the regional lymph glands. Virus has frequently been isolated from adenoid or tonsillar tissue from persons without clinical signs of acute illness; they multiply readily and produce distinctive cytopathic effects in tissue cultures of certain types of human and simian cells; they have a common antigen, demonstrable in the complement-fixation test; they fall into specific antigenic types that are demonstrable by the neutralization test; none of them has, as yet, produced manifest illness in commonly used laboratory animals.

Proposals were also made with respect to the terminology of the diseases caused by these viruses; these are in keeping with the usual practice of employing a clinical diagnostic term followed by the etiologic identification. The following examples were given: acute respiratory disease caused by adenovirus type 4; pharyngitis or pharyngoconjunctival fever caused by adenovirus type 4; follicular conjunctivitis caused by adenovirus type 6; keratoconjunctivitis caused by adenovirus type 8; or pneumonitis or atypical pneumonia caused by adenovirus type 7. It was believed that such terminology would eliminate the confusion that might arise from the fact that a single serotype can produce clinically different diseases, and, conversely, that clinically similar illnesses may be produced by different adenovirus serotypes as well as by unrelated agents.

The avoidance of any new abbreviation in the recommendation for the new group name for the respiratory-tract viruses and for the designations of the diseases caused by them seems particularly designed to suit the editorial policies of this *Journal,* in which the "cryptogrammic avalanche of initials" that has made alphabet soup so unpalatable has recently been decried.[6]

REFERENCES

1. Rowe, W. P., et al. Isolation of cytopathogenic agent from human adenoids undergoing spontaneous degeneration in tissue culture. *Proc. Soc. Exper. Biol. & Med.* **84**:570-573, 1953.
2. Hilleman, M. R., and Werner, J. H. Recovery of new agent from patients with acute respiratory illness. *Proc. Soc. Exper. Biol. & Med.* **85**:183-188, 1954.

3. Huebner, R. J., et al. Adenoidal-pharyngeal-conjunctival agents: newly recognized group of common viruses of respiratory system. *New Eng. J. Med.* **251**:1077-1086, 1954.
4. Enders, J. F., et al. "Adenoviruses": group name proposed for new respiratory tract viruses. *Science* **124**:119, 1956.
5. Rowe, W. P., Hartley, J. W., and Huebner, R. J. Additional serotypes of APC virus group. *Proc. Soc. Exper. Biol. & Med.* **91**: 260-262, 1956.
6. Editorial. Alphabet soup. *New Eng. J. Med.* **254**:1007, 1956.

SAFETY IN FLIGHT

A RECENT report from Metropolitan Information Service of the Metropolitan Life Insurance Company on safety in air travel on United States scheduled domestic lines reads almost like an advertisement for aerial travel. According to a study by Metropolitan's well known statisticians, safety in this method of travel has progressed to the point where the fatality rate per 100,000,000 passenger miles is less than a tenth what it was only twenty years ago.

Thus, for the years 1953 through 1955 the rate was 0.55 per 100,000,000 passenger miles traveled, compared with a rate of 5.87 for 1933 through 1935, the figures being derived from Civil Aeronautics Administration data. Furthermore, the number of miles flown in the last three years is eighty times that of the period of comparison in the 1930s. No statement was made regarding the number of lives actually lost.

International operations, the statisticians aver, show an even more striking factor of safety, only 4 passenger deaths having occurred in such flights on United States scheduled air lines in 1953, 1954 and 1955. This represents a fatality rate of only 0.03 per 100,000,000 passenger miles, which is considerably better than scheduled foreign lines have yet been able to achieve.

The factors to which this improvement is attributed include better planes than before, with better equipment, better-trained pilots and crews, better airfields with better communication facilities and better reporting of weather. A practical evidence of this greater security is the acceptance of passengers at standard rates by life-insurance companies, a policy that has even begun to apply to pilots and members of crews. This must be comforting information to those who travel by air or are contemplating flying, in view of the catastrophes that appear so unexpectedly and so tragically in the news.

No comparison is made in the release, in respect to numbers involved and either distances traveled or time spent in travel, with railroads, steamship lines or scheduled bus trips.

It would seem, in view of relative speeds of travel, that some additional factor or factors should be considered in an evaluation of safety, and not simply the distance covered. It might appear to some persons, perhaps statistically naïve, that the important factor should be the number of passengers who lose their lives each year as a result of flying accidents, in relation to the number who take to the air. For the number of miles traveled is a matter of speed and not of the risk involved per hour of being airborne or of taking off and landing.

If distance were the real criterion then the slowest methods of travel, such as pedestrianism, might entail the greatest risk because of the fantastically longer time required to attain the same mileage while thus earthborne.

It may also be of some significance that in the training of pilots the hours of flying rather than the distance covered is used as the standard by which experience is measured.

Died — In Athol, Mass., August 14th, by being thrown from his carriage, Dr. H. B. Austin, of that place.

Boston M. & S. J. *August 28, 1856*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

AFIBRINOGENEMIA AFTER RUPTURE OF THE UTERUS

A twenty-seven-year-old woman, with 2 previous normal deliveries and a completely uneventful prenatal course, entered the hospital in early labor when thirty-nine weeks pregnant. The membranes were intact. Seven hours later a physician found her in active labor, with the cervix dilated 4 cm. and the membranes bulging. Demerol and Seconal were given. No oxytocics were administered. About five minutes later the membranes ruptured spontaneously, and tumultuous labor followed. On re-examination the cervix was found to be fully dilated.

Spinal anesthesia (Pontocaine, 5 mg.) was given for delivery at 10:24 p.m. During stabilization of the spinal anesthesia the fetal heart beat was lost, and sudden vaginal bleeding began. After a hurried draping the examiner found the fetal head in the pelvis, but the feet were beside it, in a jackknife position. Internal podalic version was therefore elected and immediately accomplished without difficulty, producing a stillborn infant, weighing 3.2 kg. (7 pounds), at 10:45 p.m.

The physician attempted to resuscitate the baby for about ten minutes, and then turned his attention to the mother, only to find her condition critical. The placenta, not yet separated, was extracted manually, and a rupture of the right side of the uterus was discovered. Supravaginal hysterectomy and repair of a laceration of the bladder were started at 11:20 p.m. and completed in an hour. The uterus had been ruptured up the entire right side from cervix to fundus.

In spite of blood, plasma expander, nor-epinephrine and Levophed the pulse and blood pressure were

imperceptible during surgery. Postoperatively, despite multiple transfusions and supportive treatment, dusky cyanosis persisted with 100 per cent oxygen, but there was no respiratory difficulty. Bleeding from the vagina and catheter continued, and the abdominal wound oozed freely. After three and a half hours it was noted that blood taken for the original crossmatch had failed to clot, so fibrinogen was obtained. By this time the patient was moribund, but more blood and fibrinogen were given under pressure, and in three more hours a few clots were present on the perineal pad for the first time. However, she died in profound shock at 10:50 a.m. while receiving her thirteenth transfusion. Permission for autopsy was refused.

This case was classified as a nonpreventable death due to afibrinogenemia, the contributing cause being a probable amniotic-fluid infusion through the laceration caused by rupture of the uterus, which was presumably spontaneous and must have occurred when the membranes ruptured during tumultuous labor. There may have been an unrecognized malpresentation before this, or the jackknifing may have coincided with sudden loss of fluid if the presenting part was high. Certainly, this combination could cause uterine rupture, which need not be attributed to the internal podalic version. In fact, it is said that this was done without any resistance at all, suggesting that the rupture had already occurred.

Although operation was performed with reasonable promptness and no effort was spared, teamwork broke down twice: when the patient's condition became critical during the ten minutes of fruitless resuscitation an alert anesthetist might have given due warning while the obstetrician necessarily had his attention seriously diverted (a few moments saved here would have been invaluable); and, while the operating staff struggled with surgery, shock and blood loss, a clot was casually noted by a technician to dissolve, but this was not reported for more than three hours. True, a clinician is always responsible for making his own observations, but many a skilled surgeon owes his success to alert assistants. In this case, it is now obvious that the intravenous infusion of amniotic fluid not only resulted in profound shock but also caused, as it often does, afibrinogenemia. Copious transfusion accompanied by fibrinogen at the time of the hysterectomy itself — namely, at about 11:30 p.m., rather than three and a half hours later — might have saved this patient. It is hard to see how the surgeon in charge, already working desperately against time and overwhelming odds, could have personally observed clot dissolution in the specimens taken for crossmatching; it is regrettable that the laboratory technicians did not call this to his attention.

JOHN FIGGIS JEWETT, M.D.
Chairman

Boston

CORRESPONDENCE

THAT CLINCHES IT

To the Editor: The following letter is offered in partial reply to the letter of Dr. Le Compte, published in the August 2 issue of the *Journal*:

Dear Doctor:

Here I've been living the life of Riley for the past four years after recovering from a coronary. No hard work; even 84 year old grandma sees that others carry all the packages. Then when I do work in the garden for a half hour I'm urged to sit myself in the shade to enjoy a cooling drink.

But, why did you have to tell the reporters that this was all hooey and that I could even shovel snow? What a let down! Couldn't you write the Ames Tribune that the reporters misunderstood you; that that was just for young healthy fellows not for guys older than Eisenhower. You sure spoiled it, the life of Riley; what a memory! Back to the old grind.

You never lived with a woman who tried to keep you from becoming bored over the weekend. For the past forty years until the coronary deal there was a bulletin board in the kitchen of things to be done over the weekend. Now, since your newspaper statement the board is back up. Doctors can be useful, but woe is me, that a doctor of your repute should tell my wife what is good for me. . . . That's the clincher. Doctor why did you do it, it was so nice while it lasted.

Very truly yours,
A. W. RUDNICK
214 So. Russell
Ames, Iowa

PAUL D. WHITE, M.D.

BOOK REVIEW

A Textbook of Neurology. By H. Houston Merritt, M.D. 8°, cloth, 746 pp., with 181 illustrations and 128 tables. Philadelphia: Lea and Febiger, 1955. $12.50.

This new textbook of neurology is a thoroughly up-to-date monograph with certain features that make it an important addition to the medical literature. The author, who is director of the Neurological Institute in New York City, is thoroughly qualified to write such a book. Moreover, he has made certain changes, deviating from the usual textbooks, that make his volume distinctive. The traditional sections on anatomy and examination of the nervous system have been omitted. He is quite right in assuming that these no longer have a legitimate place in a textbook intended primarily for students and general practitioners. Also, other books cover these two fields adequately. Secondly, and of more importance, he has made a radical change in omitting any consideration of the psychoneuroses or so-called functional psychoses. Thus, the traditional link between neurology and psychiatry has been cut, and most will agree with the author regarding the appropriateness of his decision.

In general, diseases are grouped on an etiologic basis. The principal syndromes of neurology are adequately described, with a few well chosen illustrations and references to the pertinent literature. This book is so excellent that adverse criticism is reduced to a minimum. A few of the illustrations could be improved, particularly those depicting clinical signs, and there is a slight tendency, common in many books, to overemphasize the rare and unusual. Considering that the book is less than 750 pages in length, an amazing amount of information is contained in it. From the medical student particularly, it should receive a warm welcome. Al-

though there are a number of other books of approximately the same size, covering the same material, none are more comprehensive or more satisfying.

HENRY R. VIETS, M.D.

NONCLINICAL NOTES

UNIVERSITY OF MICHIGAN MEDICAL SCHOOL

More than 600 medical alumni of the University of Michigan Medical School will meet in Ann Arbor, September 27-29 for their Triennial Medical Alumni Conference.

Dean A. C. Furstenberg of the School cordially invites every Michigan Alumnus to attend this sixth such conference of its kind since 1938. Information on housing, program, reservations, and so forth may be obtained by writing to Dean A. C. Furstenberg, University of Michigan Medical School, Ann Arbor, Michigan.

NOTICES

SOUTH END MEDICAL CLUB

The monthly meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, September 18, at 12 noon.

Dr. Lionelle D. Wells will talk on "Organ Neuroses."

ACADEMY OF PSYCHOSOMATIC MEDICINE

The Academy of Psychosomatic Medicine will hold its third annual meeting at the Hotel Plaza, New York City, October 4, 5 and 6, 1956. The over-all subject of the meeting will be the psychosomatic aspects of the general practice of medicine.

MISSISSIPPI VALLEY MEDICAL SOCIETY AMERICAN MEDICAL WRITERS' ASSOCIATION

The Mississippi Valley Medical Society will hold its twenty-first annual convention, dedicated to general practitioners, at the Hotel Morrison, Chicago, September 26-28, 1956. On September 28 and 29 the annual meeting of the closely affiliated American Medical Writers' Association will take place. Those interested in either event should write to the secretary, Dr. Harold Swanberg, 209-224 W. C. U. Building, Quincy, Illinois.

AMERICAN PUBLIC HEALTH ASSOCIATION

The eighty-fourth annual meeting of the American Public Health Association will be held at Atlantic City, November 12 to 16, 1956.

AMERICAN GOITER ASSOCIATION

The Van Meter Prize Award of $300 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland will be presented at the annual meeting of the American Goiter Association at the Hotel Statler, New York City, May 28-30, 1957. Essays must be received by the Secretary not later than January 15, 1957. Further information may be obtained from Dr. John C. McClintock, Secretary, 149 Washington Avenue, Albany 10, New York.

SOCIETY MEETINGS AND CONFERENCES

AUGUST 19–23. American College of Chest Physicians. Page 840, issue of November 10.
AUGUST 24 and 25. National Hemophilia Foundation. Page 249, issue of August 2.
AUGUST 27 and 28. Consultation Clinics for Crippled Children in Massachusetts, Page 1244, issue of June 28.
SEPTEMBER 3–5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.
SEPTEMBER 3–7. First Inter-American Conference on Occupational Medicine and Toxicology. Page 152, issue of July 19.
SEPTEMBER 8, 9 and 10. Vermont Heart Association and University of Vermont College of Medicine. Page 360, issue of August 16.
SEPTEMBER 9–13. International College of Surgeons. Page 304, issue of August 9.
SEPTEMBER 18. South End Medical Club. Notice above.
SEPTEMBER 19 and 20. San Diego Postgraduate Assembly. Page 360, issue of September 16.
SEPTEMBER 28 and 29. Mississippi Valley Medical Society and American Medical Writers' Association. Notice above.
OCTOBER 4, 5 and 6. Academy of Psychosomatic Medicine. Notice above.
OCTOBER 7, 8 and 9. New Hampshire and Vermont State Medical Societies. Page 304, issue of August 9.
OCTOBER 8–13. International Cancer Cytology Congress. Page 104, issue of July 12.
OCTOBER 15–26. New York Academy of Medicine. Page 304, issue of August 9.
OCTOBER 19 and DECEMBER 14, 1956, and FEBRUARY and APRIL, 1957. Massachusetts Society for Research in Psychiatry. Page 56, issue of July 5.
OCTOBER 30 and 31 and NOVEMBER 1. New England Postgraduate Assembly, Boston.
NOVEMBER 12–16. American Public Health Association. Notice above.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, AUGUST 30

THURSDAY, AUGUST 30
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. Tumors of the Lung. Dr. Harrison Black. Main Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, AUGUST 31
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Urological Conference. Dr. C. J. E. Kickham, presiding. Auditorium, Carney Hospital, Dorchester.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, SEPTEMBER 1
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.

(Concluded on page xx)